DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 208, 314, and 601

[Docket No. 93N–0371]

RIN 0910–AA37

Prescription Drug Product Labeling; Medication Guide Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: Inadequate access to appropriate patient information is a major cause of inappropriate use of prescription medications, resulting in serious personal injury and related costs to the health care system. The Food and Drug Administration (FDA) believes that it is essential that patients receive information accompanying dispensed prescription drugs. This information must be widely distributed and be of sufficient quality to promote the proper use of prescription drugs. Therefore, FDA is proposing performance standards that would define acceptable levels of information distribution and quality, and to assess supplied information according to these standards. Preliminary evidence suggests recent increases in the distribution of privately-produced patient medication information with dispensed prescriptions. Unfortunately, estimated distribution rates indicate that significant portions of patients do not receive information with their medications. FDA analyses also indicate that there is a high variability in the quality of this information. FDA believes that, with greater encouragement and clear objectives, the private sector will substantially improve the quality and distribution of patient information. Therefore, in concert with Healthy People 2000, FDA is proposing that private sector initiatives meet the goal of distributing useful patient information to 75 percent of individuals receiving new prescriptions by the year 2000 and 95 percent of individuals receiving new prescriptions by the year 2006. FDA is proposing two alternative approaches to help ensure that these goals (performance standards) are achieved. FDA would periodically evaluate and report on achievement of these goals. If the goals are not met in the specified timeframes, FDA would either (1) Implement a mandatory comprehensive Medication Guide program, or (2) seek public comment on whether the comprehensive program should be implemented or whether, and what, other steps should be taken to meet patient information goals. Regardless of the approach chosen, a mandatory Medication Guide program limited to instances where a product poses a serious and significant public health concern requiring immediate distribution of FDA-approved patient information would be implemented within 30 days of publication of a final rule based on this proposal. FDA believes that substantial health care cost savings can be realized by ensuring that consumers obtain the inherent benefits of proper use of prescription drugs, and by reducing the potential for harm caused by inappropriate drug use by the patient.

DATES: Comments by November 22, 1995.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Louis A. Morris, Center for Drug Evaluation and Research (HFD–240), Food and Drug Administration, 5600 Fishers Lane Rockville, MD 20857, 301–594–6828.

SUPPLEMENTARY INFORMATION:

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I. Introduction

As the Federal agency responsible for the proper labeling of prescription drug and biological products, FDA believes that patient information accompanying these products is essential. It is paradoxical that products as potentially hazardous as prescription medications are often dispensed with little more than a ''use as directed'' statement printed on the container label. Considerably less dangerous products, such as foods and over-the-counter (OTC) drugs, contain extensive usage labeling. Many OTC drugs also contain detailed warning labeling. Further, food labeling serves to warn at-risk individuals of potentially harmful ingredients. For example, people with phenylketonuria need to know what foods contain phenylalanine. Similarly, people with diabetes need to know about sugar content and people with high blood pressure need to know about sodium content.

FDA believes that improved dissemination of accurate, thorough and understandable information about prescription drug products is necessary to fulfill patients' need and right to be informed. Regardless of any other effects of such information, FDA believes that the direct educational benefits are sufficient to justify a requirement that such information be disseminated.

The use of drug and biological products often entails complex risk-benefit deliberations by prescribers. Yet, there is often little or no information shared with patients about the treatment's potential outcomes (i.e., its risks and benefits). In contrast, even simple surgical procedures, often posing

less severe risks to the patient, routinely require detailed patient consent prior to instituting the procedure. Improved education will enhance patients' ability to understand the benefits and risks of treatment. This will help patients interact more fully with health care professionals, thereby enabling patients to take a more active role in their own health care.

FDA also believes that improved patient education will improve adherence with prescribed regimens, decreasing unnecessary physician visits and hospitalizations, and will give patients the information they need to make truly informed decisions about the drugs they take. Demographics suggest an increasing need for better information and counseling about drugs. As the population ages, a greater proportion will rely heavily on prescription drugs.

It has been over a decade since FDA withdrew regulations mandating patient package inserts (PPI's) for prescription drugs. (PPI's are leaflets containing information about a drug product's benefits, risks, and directions for use.) At that time, the agency stated that mandatory requirements were unnecessary because the goal of improved patient education could be achieved through private sector initiatives. During this period, numerous voluntary programs designed to improve patient knowledge were launched, many with direct support from FDA and virtually all with FDA encouragement. In addition, FDA has asked certain manufacturers to include patient labeling for a few prescription drugs, where FDA believed that it was essential that patients were directly informed about the products' risks and limitations.

In the decade following withdrawal of the PPI regulations, FDA conducted research to evaluate the progress made by the voluntary programs. This research has shown minimal progress in improving the distribution of prescription drug information to patients.

However, very recently there have been new and encouraging signs that a greater percentage of patients are now receiving written information with their prescriptions. Many State Boards of Pharmacy expanded the offer to counsel requirement of the Omnibus Budget Reconciliation Act of 1990 (OBRA '90) to include all patients, instead of only Medicaid recipients. Developments in computer technology have permitted pharmacies more effectively to store and generate written documents for patients. As a result, there appears to be a sharp increase in the number of patients receiving computer-generated information along with their medication.

FDA is encouraged by this recent trend and hopes that: (1) It continues so that eventually the vast majority of Americans will receive this vital information, and (2) the information dispensed will be sufficiently accurate, thorough, and understandable for patients to properly use and monitor their treatment.

Therefore, in concert with goals established by the Public Health Service's Healthy People 2000, FDA is proposing performance standards for the distribution and quality of voluntary written prescription drug information dispensed to patients. Achievement of these performance standards would indicate that there is no need for Federal regulations for a comprehensive mandatory patient information program. Failure to achieve these performance standards would indicate that a federally-mandated comprehensive patient information program is necessary to meet patients' prescription drug information needs. In this document, FDA is proposing for public comment two alternative approaches that could be used to encourage achievement of performance standards for quality and distribution of patient prescription drug information, and to ensure that those products that pose a serious and significant public health concern include FDA-approved patient labeling. If the private sector fails to attain the performance standards in the specified timeframes, both alternatives would ultimately result in a regulation that would require that FDA-approved patient labeling be prepared and dispensed to patients, along with new prescriptions, for most prescription drug products used primarily on an outpatient basis. The alternatives are described in detail in section VIII. of this document.

FDA will continue to monitor and evaluate progress toward the standards for a 5- to 11-year period. During this time, FDA will continue to work with and encourage private sector efforts to educate patients. It is FDA's hope and belief that a renewed partnership to encourage voluntary distribution of prescription drug information, coupled with feedback and accountability, is the best mechanism for achieving the goal of improved patient information.

Currently, although numerous sources of prescription drug information suitable for distribution to patients have been developed, sizeable proportions of patients have not received adequate written information. With the advent of patient information software and installation of computer systems in pharmacy outlets, FDA believes that acceptable levels of patient information can result from voluntary efforts if three important conditions are instituted. First, there must be clearly established and attainable goals. Second, there must be sufficient incentives to achieve these goals. Third, for selected products, which cannot be marketed for safe and effective use unless patients receive clear warnings and directions, patient labeling (Medication Guides) must be required.

To promote responsibility and accountability, FDA is proposing performance standards for both the distribution and quality of written information. Performance standards would permit the flexibility demanded by an ever-changing, complex, and diverse distribution system for product information, while ensuring consistency in the application of standards.

Performance standards would result in less burdensome requirements on drug manufacturers and dispensers, the flexible adaptation of product information requirements into broader patient education programs, and increased utilization of technology to improve storage and distribution of information. They would further encourage a partnership approach so that health care providers, drug manufacturers, patient/consumer groups, and the public sector can work cooperatively to provide essential information to patients. If these standards are met, a comprehensive program of FDA-approved patient labeling would not be required. If these clearly defined and achievable performance standards are not met within a reasonable time period, FDA will institute steps to help ensure that the standards will be achieved.

During the hearings that led to the withdrawal of the 1980 PPI regulations, promises were made by representatives of the pharmaceutical, medical, and pharmacy communities that if FDA withdrew the PPI regulations, the private sector would develop a variety of systems that would meet the goals of the proposed PPI program. These promises have not yet been fulfilled. In the withdrawal notice, FDA promised to monitor periodically and evaluate progress made in providing patients with necessary prescription drug information. However, the withdrawal notice did not contain specified goals or a time frame for evaluating progress toward these goals.

While FDA understands and accepts that the development of grassroots programs will necessarily take longer than a mandatory program, FDA

believes that the continuation of an open-ended promise without a clear time frame for judging success is unacceptable. Therefore, FDA intends to articulate clear distribution and quality goals and maintain a specific timetable for judging success. During this time, FDA will only require FDA-approved patient labeling for certain drugs for which patient information will greatly facilitate safe and effective product use.

FDA has found that there are certain prescription drugs for which patient information is integral to the very marketing of the products. For these products, patient information is essential to assure that the drug can be used with acceptable levels of risk. Historically, PPI's have been instituted by independent regulations (e.g., estrogen products, oral contraceptives) or on a voluntary basis by the manufacturer (e.g., Accutane, Halcion, Proscar, Metformin). FDA has concluded that PPI's were essential for specific drug products based upon the existence of significant and possibly life-threatening drug effects about which patients must be warned in order to understand the risks they are undertaking by using the product or how to minimize those risks (e.g., by carefully monitoring their response to treatment for signs of adverse drug effects). These considerations are based upon a broad safety analysis that includes the indication for the product, the existence of alternative treatments, and the potential for patient information to increase the margin of safety in using the product.

While FDA has usually successfully relied upon the good will and voluntarism of prescription drug manufacturers to institute PPI's when needed, there have been occasions where manufacturers have refused to include such information. For example, although one manufacturer of a particular drug agreed to include a PPI when new information was uncovered about the possibly fatal interaction of this product with certain other products, the manufacturer of a similar product in the same therapeutic class, for which the same drug-interaction warning applied, did not agree to provide patients with a PPI.

As the agency has done with estrogens and oral contraceptive drug products, FDA could rely on notice and comment rulemaking to require patient labeling when necessary. However, it takes a significant amount of time to propose and finalize such regulations. Therefore, FDA is proposing rules that would require patient labeling (Medication Guides) for certain products that pose a serious and significant public health concern requiring immediate distribution of FDA-approved patient information.

II. Regulatory Background

A. Brief History of Patient Labeling Initiatives and the 1980 Final Rule on Patient Package Inserts

Since 1968, FDA has occasionally required that labeling written in nontechnical language be distributed to patients whenever certain prescription drugs were dispensed. Generally, FDA required distribution of such patient information to alert patients of adverse reactions associated with the drug product or to provide information about the product's use, contraindications, precautions, and effectiveness. Examples of such patient-oriented labeling include patient warnings on isoproterenol inhalation drug products (see 33 FR 8812, June 18, 1968), oral contraceptive drug products (see 35 FR 9001, June 11, 1970, and 43 FR 4212, January 31, 1978), estrogenic drug products (see 42 FR 37636, July 22, 1977), and patient labeling requirements for progestational drug products (see 43 FR 47198, October 13, 1978). (FDA has also approved patient labeling as part of the labeling requirements for certain individual drug products. These products include Roferon, Introna, Nicoderm, Nicorette, Rogaine, Halcion, Norplant System, Proscar, Accutane, and others.)

During the 1970's, FDA also began evaluating the usefulness of patient labeling for prescription drug products generally, and studied ways to present the information to patients. FDA discussed patient labeling issues with interested and potentially affected persons, reviewed scientific literature about patients' needs and desires for patient labeling, conducted research projects to evaluate existing and model patient labeling pieces, and reviewed existing methods for communicating drug information to patients (44 FR 40016 at 40018–40025, July 6, 1979, and 45 FR 60754 at 60755–60758, September 12, 1980). FDA also published a notice in the **Federal Register** of November 7, 1975 (40 FR 52075), soliciting public comments to assist the agency in formulating a policy on patient labeling.

As a result of these initiatives, in the **Federal Register** of July 6, 1979 (44 FR 40016), FDA issued a proposed rule to require PPI's for prescription drug products. The proposal would have required manufacturers or distributors to prepare PPI's for their drug products. Persons dispensing the drug products would be required to distribute the PPI's to patients. The PPI would be in nontechnical language, would not be promotional in tone or content, would be based primarily on the approved professional labeling, and:

> * * * would contain both a summary of the information about the product and more detailed information that identifies the product and the person responsible for the labeling, the proper uses of the product, circumstances under which it should not be used, serious adverse reactions, precautions the patient should take when using the product, information about side effects, and other general information about the proper uses of prescription drug products.

(44 FR 40016 at 40025).

The 1979 proposed rule would have required PPI's to be distributed to the patient with the drug product except in limited situations, such as those where the patient was legally incompetent or when institutionalized.

The 1979 proposal generated approximately 1,500 comments. Generally, consumers favored the proposed PPI program, but many licensed practitioners, pharmacists, and drug manufacturers opposed it. Those in favor of a mandatory PPI program contended that it would: (1) Promote patient understanding of and adherence to drug therapy; (2) permit the patient to avoid interactions with other drugs or foods; (3) prepare the patient for possible side effects; (4) inform the patient of positive and negative effects from the use of the drug product; (5) permit the patient to share in the decision to use the drug product; (6) enhance the patient/licensed practitioner relationship; and (7) provide the pharmacist and licensed practitioner with a basis for discussing the use of a prescription drug product with the patient. Those opposed to the program contended that it would: (1) Encourage self-diagnosis and the transfer of prescription drug products between patients; (2) produce adverse reactions in patients through suggestion; (3) affect adversely the liability of drug manufacturers, licensed practitioners, and pharmacists; (4) interfere with the patient/licensed practitioner relationship; (5) impose unnecessary burdens on manufacturers and pharmacists; and (6) increase the cost of prescription drug products and health care in general.

After considering the comments, in the **Federal Register** of September 12, 1980 (45 FR 60754), FDA published a final rule that established requirements and procedures for the preparation and distribution of PPI's. FDA concluded that there was ample evidence that PPI's can significantly improve the quality of health care obtainable from using prescription drugs. The agency

explained that PPI's can reduce the potential for harm to patients resulting from prescription drug use by enhancing patient compliance with prescribed regimens and by decreasing inappropriate drug use. In addition, PPI's can increase patient knowledge about prescription drugs, thereby promoting their optimal use.

The 1980 final rule required PPI's for human prescription drug products, and, as in the 1979 proposed rule, required manufacturers and distributors of prescription drug products to prepare PPI's for their drug products. The 1980 final rule required distributors and dispensers to distribute the PPI's to patients receiving a new prescription, but did not require PPI distribution for prescription drug refills or where the patient's licensed practitioner specifically directed that the PPI not be given to the patient (unless the patient specifically requested it). The 1980 final rule required a PPI to be written in nontechnical language, be based primarily on the approved professional labeling for the drug product, and contain: (1) The drug product's established name or, for a licensed biological product, proper name; (2) a summary of the information about the drug product; (3) a statement about the proper use of the drug product, identifying its indications for use; (4) information which the patient should provide the health practitioner before taking the drug, including the circumstances under which the drug product should not be used; (5) a statement of serious adverse reactions and potential safety hazards; (6) caution statement(s) that patients should observe, including statements about risks to pregnant women, nursing mothers, and pediatric patients; (7) a statement of the risks, if any, to the patient of developing a tolerance to or dependence on the drug; (8) a statement of what the patient should do in case of overdose or missed doses; (9) a statement of clinically significant, frequently recurring, possible side effects; (10) information about the safe and effective use of prescription drug products; and (11) information about the drug product's manufacturer, packer, or distributor, special storage instructions, and the PPI's date (45 FR 60754 at 60781–60782).

Under the 1980 final rule, manufacturers, distributors, or dispensers would provide PPI's to ''practitioners, pharmacists, other dispensers and consumers'' in ''sufficient numbers'' to permit a party to provide a PPI to each patient receiving a drug product. However, the 1980 final rule also permitted distributors and dispensers to prepare and use their own PPI's. The 1980 final rule also contained provisions that would require health care institutions to make PPI's available to patients upon the patient's request, after notification of availability. It would not have required PPI's for patients receiving emergency treatment.

The 1980 final rule provided printing specifications, and stated that FDA might prepare and make guideline PPI's available for specific drugs or drug classes. In the **Federal Register** of September 12, 1980 (45 FR 60785), FDA issued draft guideline PPI's for 10 drugs or drug classes. The 10 drugs or drug classes were: Ampicillin, benzodiazepines, cimetidine, clofibrate, digoxin, methoxsalen, propoxyphene, phenytoin, thiazide, and warfarin. FDA intended to implement PPI's for these 10 drugs or drug classes over a 3-year period, after which the agency would evaluate the program's results before applying the requirements to additional drugs. FDA stated that, although there was ample evidence of the value of PPI's in helping patients use drug products safely and effectively, additional studies were needed to confirm the costs of a mandatory, nationwide PPI program, to determine whether those costs were reasonable in terms of the benefits the program provides, and also to verify the best way to convey to consumers information about prescription drug products. In the **Federal Register** of November 25, 1980 (45 FR 78516), FDA announced that the PPI requirements would be effective on May 25, 1981, for cimetidine, clofibrate, and propoxyphene. In the **Federal Register** of January 2, 1981 (46 FR 160), the agency announced that the requirements for ampicillin and phenytoin would be effective on July 1, 1981. FDA issued final PPI's for these five drugs. The agency did not establish an effective date for the remaining five drugs.

B. The Stay of Effectiveness for the 1980 Final Rule and Its Subsequent Revocation

On February 17, 1981, the President issued Executive Order 12291 (see 46 FR 13193, February 19, 1981). Section 2 of the Order required each Federal agency to adhere to certain principles in promulgating new regulations and reviewing existing regulations. Given this Executive order, the Department of Health and Human Services and FDA decided to review the 1980 final rule. In the **Federal Register** of April 28, 1981 (46 FR 23739), the agency stayed the effective date for the 1980 final rule because it had received numerous comments stating that PPI's would be unnecessarily burdensome, costly, and inconsistent with Executive Order 12291. In the same issue of the **Federal Register**, FDA stayed the effective date of the PPI's. FDA indicated that further review of the PPI program was necessary. On September 30 and October 1, 1981, the agency held public meetings on the PPI program. The meetings reviewed FDA's administrative record of the PPI program and the results of a 3-year study conducted for FDA by the Rand Corp. on PPI's of various styles and formats.

On the basis of its review, in the **Federal Register** of February 17, 1982 (47 FR 7200), FDA proposed to revoke the 1980 final rule. The agency stated that:

> The goals of providing patients with information about prescription drugs can be reached more effectively and efficiently by cooperating with health professionals and others in both the public and private sector to expand upon current initiatives in patient education.

FDA reiterated its belief that informing patients about their prescription drug products would significantly improve the quality of their health care, and established a Committee on Patient Education to coordinate efforts to educate consumers about prescription drugs and to help private sector initiatives. However, the agency believed that private sector initiatives would be more effective than a mandatory PPI program and should be encouraged (see 47 FR 7200 at 7201).

In the **Federal Register** of September 7, 1982 (47 FR 39147), the agency issued a final rule that revoked the PPI regulations. The revocation was based, for the most part, on a decision to permit voluntary private sector initiatives for distributing patient information to proceed before a determination was made whether to impose a mandatory program. The preamble to the final rule listed several private sector programs underway at that time: (1) The National Council on Patient Information and Education (NCPIE)—a national consortium of health professionals, trade representatives, consumer groups, and Government agencies formed to encourage, coordinate, and promote private patient education efforts; (2) the American Medical Association (AMA) distributed Patient Medication Instruction (PMI) sheets—drug information leaflets to be handed out by licensed practitioners at the time of prescribing; (3) the American Society of Hospital Pharmacists, now known as the American Society of Health-Systems Pharmacists (ASHP), designed publications and audiovisual

presentations to assist hospital and retail pharmacists in providing drug information to patients; (4) the United States Pharmacopeial Convention, Inc. (USP), published several consumer guides to prescription drugs; (5) the American Association of Retired Persons (AARP) provided package inserts with prescriptions filled by its mail-order pharmacy service; (6) Doubleday, Inc., published a consumer's compendium of drug therapy, which included tear-out sheets about specific diseases; and (7) many retail pharmacies provided pamphlets, posters, and books on prescription drugs to pharmacy customers (47 FR 39147 at 39151). Some of these programs and others are discussed in detail below.

In the preamble to the final rule FDA stated:

> * * * Although the agency realizes that consumer groups generally supported the PPI pilot program, it believes that as the voluntary systems emerge, consumers will receive not only an adequate supply of prescription drug information from a variety of sources, but should receive more information about more drugs than would have resulted from a mandatory system. FDA also believes that the current regulatory environment demands that these various private sector efforts be given the opportunity to demonstrate that they can meet consumers' needs as well, if not better than, a government program.

(47 FR 39147 at 39153).

FDA indicated that, although it was revoking the 1980 regulation, it intended to work closely with the private sector and with other public sector agencies to identify and implement methods of providing information about prescription drugs to consumers, to promote patient education, to monitor changes in patient awareness of drug information, and to develop and evaluate the effectiveness of information dissemination activities. As mentioned above, FDA announced that it was forming a Committee on Patient Education to coordinate efforts to educate consumers about prescription drugs and to serve as a catalyst for private sector initiatives. Specifically, the committee was established to: (1) Evaluate existing patient information systems as well as new ones; (2) encourage the formation of, and serve as a liaison for, outside organizations that are or want to become active in patient information systems; (3) provide guidance and serve as a clearinghouse for firms that want to draft prescription drug information; (4) alert consumers and health professionals to the usefulness and availability of prescription drug information; and (5) identify the need for patient information in the use of other FDA-regulated products. FDA also indicated that it would be conducting surveys of consumers and health care professionals to evaluate the availability of adequate patient information on a nationwide basis. FDA stated that it will assess this information ''over the next several years.'' FDA also noted: ''The agency believes it would be counterproductive to the development of private initiatives for it to develop and publicly announce a course of action it might take should these private initiatives not materialize'' (47 FR 39147 at 39152).

III. The Continuing Need for Prescription Drug Information

A. Continuing Problems of Lack of Adherence and Preventable Adverse Drug Reactions

FDA's proposal and final rule extensively reviewed the literature relating to patient adherence (also known as compliance) with medication regimens. FDA cited two literature reviews, and completed its own review of 50 studies, and concluded that noncompliance rates averaged from 30 percent to 50 percent. FDA also concluded that improved communication could contribute to improving compliance rates. Written information was necessary not only to improve adherence rates, but to inform patients about precautions, contraindications, and adverse drug reactions, leading to better knowledge about: (1) Using drugs properly, (2) monitoring reactions to medications for signs of possible problems, and (3) raising issues with licensed practitioners and other health professionals to improve communications about medication. (The term ''licensed practitioner'' in this document refers to individuals licensed, registered, or otherwise permitted to prescribe drug products in the course of their professional practice.)

The literature published since 1982 continues to support the conclusion that patient education can contribute to the prevention of disease, successful results in treatment, and reduction in medical costs. However, the need for drug information, education, and counseling exceeds the current supply, both in quantity and quality, and much of the available information fails to reach patients who need it, when they need it, and in the form they need it (Ref. 1). Although there is a wide variety of sources, the information that actually reaches most patients is focused primarily on how to use the medication, with little precautionary or adverse drug information obtained by most patients (Ref. 2). FDA believes that standard drug information, when combined with counseling from a prescribing practitioner, pharmacist, or other health professional should significantly increase patients' knowledge about the prescription drugs they are taking, and thereby make prescription drugs safer and more effective for consumer use.

The literature on patient compliance since 1982 continues to demonstrate a significant lack of medication adherence. For example, a 1990 report by NCPIE found that about one-third of patients fail to take their prescribed medications (Ref. 3). An overview of patient compliance studies reveals that about one-half of prescribed medications fail to produce the intended therapeutic effect because of improper use (Ref. 4). Studies examining compliance rates in specific patient populations suggest that parental noncompliance with drug therapy prescribed for their children exceeds 50 percent (Ref. 5) and noncompliance in the elderly ranges from 26 percent to 59 percent (Ref. 8).

Patient noncompliance with prescribed drug regimens can be directly related to therapeutic failure. For example, missed doses of antiglaucoma medications may lead to optic nerve damage and blindness. Missed doses of antiarrhythmic medications may lead to arrhythmia and cardiac arrest. Missed doses of antihypertensive drug products may lead to rebound hypertension that is sometimes worse than if no medication was taken at all. Missed doses of antibiotics may lead to recurrent infection and also may contribute to the emergence of antibiotic-resistant microorganisms (Ref. 9).

In addition to addressing problems of adherence, patient information is also necessary to improve drug use by forewarning patients about precautions to take to avoid adverse drug reactions. Further, forewarning is necessary to improve the patient's ability to monitor reactions to treatment to ensure both that the drug is working and that it is not causing adverse reactions.

A 1990 report by the Office of the Inspector General found that the process of patient education can save time by reducing calls or visits to the licensed practitioner or pharmacist and reducing the number of hospitalizations that are due to a patient's failure to follow his or her prescribed drug regimen (Ref. 17). For example, increased visits to the licensed practitioner may be required if the patient's condition does not improve because of noncompliance with his or her drug regimen. If the licensed practitioner is unaware of the

noncompliance, he or she may increase the patient's dosage or prescribe additional medicine that may be unnecessary and possibly dangerous. Or if the patient's condition fails to improve, the licensed practitioner may order additional diagnostic tests or unnecessary treatments.

Adverse drug reactions also are a continuing problem for the health care system. Adverse drug reactions occur in 20 percent of ambulatory patients (Ref. 10), and 2 percent to 5 percent of hospital admissions are attributed to drug-related illness (Ref. 10). The case/fatality rate from drug-induced disease in hospitalized patients is 2 percent to 12 percent (Ref. 10). Iatrogenic admissions to medical wards continue to be a costly result of improper use of prescription drugs.

At a psychiatric service of a Veterans' Administration hospital, 41 admissions over a 4-month period were reviewed for drug-related problems (Ref. 12). Two percent of admissions were determined to be due to drug side effects.

Charts of 293 patients admitted over the course of 1 year to a family medicine inpatient service were reviewed, showing 15.4 percent of admissions to be drug related (Ref. 13). Six percent of admissions for the most frequent type of drug-related admissions were for adverse drug reactions.

Adverse drug reactions among older Americans are even more frequent. In one study, researchers analyzed 463 charts of geriatric outpatients (Ref. 14), revealing 107 notations of adverse drug reactions in the charts of 97 patients (21 percent). Twelve patients were hospitalized as a direct result of an adverse drug reaction. In another study (Ref. 8) of 315 geriatric hospitalizations, 16.8 percent of admissions were determined to be related to adverse drug reactions. The hospital charge for these admissions was $224,542.

Some proportion of adverse drug reactions will occur regardless of how carefully patients follow their therapeutic regimens. Although it is difficult to estimate the proportion of adverse drug reactions and associated health care costs that can be attributed to nonoptimal patient adherence, there are some data relevant to this issue. In one study, 834 admissions to a hospital medical service were reviewed for iatrogenic disease, and 4 percent were determined to be drug-related (Ref. 11). Of these, 54 percent were classified as potentially avoidable, including, for example, overdoses and adverse reactions that evolved slowly enough that had the problems been reported earlier, treatment alterations could have been made in ambulatory care settings. In an earlier study of a sample of 1,000 patients in a community practice, it was determined that 55 percent of the adverse drug reactions experienced were unnecessary and potentially preventable (Ref. 84).

In addition, a 1990 meta-analysis of seven studies that looked at the association between hospital costs and admissions for problems specifically caused by noncompliance (strictly defined as overuse, underuse, or erratic use) indicates that adverse drug reactions caused by noncompliance constitute costly consequences for the health care system. This analysis estimated that 5.3 percent of annual hospital admissions, costing $8.5 billion in 1986, were a direct result of drug treatment noncompliance (Ref. 15).

B. The Benefits of Patient Information

1. Written Information Increases Patient Knowledge and Satisfaction

Patients who receive written information about their medications derive increased personal benefits from the information. The most widely documented of these is increased knowledge.

Industry experts, practitioners, and consumers agree that patients must have some basic information about prescription drugs to adhere successfully to their prescribed drug therapy. Many studies have tested whether the dissemination of written material increases patient knowledge and understanding. For example, a 1983 study of FDA's PPI for benzodiazepines concluded that the PPI effectively conveyed written drug information to patients, and that knowledge and comprehension varies according to the patient's age, years of education, and reading environment (Ref. 58). In this study, patients who received written patient information scored higher on a knowledge and comprehension test than those who received no written information, and those who completed the test at home scored higher than those who completed it at the pharmacy.

It is clear that patients who receive written materials about medications have increased knowledge about the use and effects of the medications (Refs. 38, 42, 44, 47, 48, 52, 53, and 59 through 61). In particular, patients who receive written information show more knowledge about side effects (Refs. 46, 47, 48, 52, and 58), and are better able to attribute adverse reactions to the medications they are taking (Ref. 62). They can more easily discriminate adverse reactions attributable to the medication from other clinical events (Ref. 63).

Patients who receive written information about their medications are more likely to make healthy lifestyle changes (Ref. 60). They are also more satisfied with their treatment (Refs. 33, 42, 47, and 53). In a review of the literature, one author suggests that provision of written materials may help patients cope with illnesses over time, as their modes of coping evolve and the corresponding need for information changes (Ref. 38).

When presented with written information about their medications, the vast majority of patients read it, particularly if it is the initial prescription (Refs. 38, 40, and 44). Reading may be thorough or superficial (Ref. 45). Patients report reading the printed information when receiving the first prescription and refills (Ref. 40), and they may read the materials more than once (Ref. 46).

2. Written Materials About Medications Can Increase Patient Compliance

Even more critical to the health care system, studies of the effects of providing written medication information to patients demonstrate that the result can be increased compliance with the treatment regimen (Refs. 38, 47, and 48). For example, in one study, outpatients who received a patient information leaflet along with their penicillin prescription were tested against patients who received no information at all. Researchers found that a significantly lower proportion of patients who received the patient information omitted doses than those who did not receive the information (Ref. 47). Similarly, researchers concluded that providing written information to patients with antibiotic prescriptions resulted in significant improvement in drug taking behavior and in knowledge about the therapy prescribed (Ref. 48). In a study of psychiatric patients, those receiving written information were more compliant in their medication regimens than those not receiving it, and patients receiving both written and oral information were the most compliant (Ref. 7). In another study, patients receiving both written and oral information about their medications were more compliant than those given no information (Ref. 49). Providing written information has also resulted in fewer patients stopping treatment (Ref. 50). The results of increased compliance may be fewer deaths and lower overall costs of treatment, due to fewer requirements for hospitalizations and

nursing home admissions (Refs. 4 and 57).

In a broad review of the effects of written information, Ley (Ref. 36) concluded that most of the studies examined found positive effects resulting from the provision of written information to patients. Out of 32 studies examining effects on knowledge, 97 percent found increases; of the 25 studies examining compliance, 60 percent found increases; and in 7 studies examining therapeutic benefit, 57 percent found increases.

It should be noted that ''compliance'' represents a broad range of behaviors that are difficult to measure (Ref. 51). Several studies that have sought to measure the effects of written information have failed to find compliance improved by written information (Ref. 44, 52 through 55). However, in a critical review of the methodologically rigorous studies of interventions to improve compliance, Haynes et al. (Ref. 56) concluded that compliance with short-term treatments can be improved by clear instructions, including written information, as well as by other interventions. Compliance with long-term treatments is more difficult to achieve; no single intervention has been shown to be effective on its own. Rather, improved compliance with long-term regimens requires a combination of interventions, including clear instructions enhanced by written information.

3. Written Patient Information Does Not Have Negative Consequences

There has been speculation about the potential adverse effects of providing information about medications to patients. However, the studies suggest that written information does not increase reports of adverse events (Refs. 38, 42, 44, 45, 48, 52, 53, 62 and 91), nor does oral information (Ref. 65). Two studies that appear to indicate the opposite are flawed. In one case, the authors admit that the written information given to patients was inadequate (Ref. 52) and, in the other, statistical analyses were performed by combining control and experimental groups inappropriately (Ref. 50). A study of psychiatric patients was inconclusive on this point (Ref. 66).

Studies do not show evidence of decreased compliance as a result of written information (Refs. 52 and 66) or evidence of increased anxiety levels (Ref. 60).

4. Relative Effectiveness of Oral and Written Patient Information

Studies examining the relative effectiveness of printed and oral medication information are scarce. However, one study shows that provision of printed information is more effective in increasing patients' knowledge than oral information, and that a combination of the two is best. The authors believe that written materials, particularly those containing information about side effects, may be more effective and timely and less alarming to patients than oral information because most side effects do not occur until after the medication has been taken for a while (Ref. 67). One author suggests that written information should be used to supplement oral instructions that should be tailored to meet the particular beliefs, concerns, and expectations of the individual patient (Ref. 38).

One meta-analysis of the literature, published in 1983 by the Pharmaceutical Manufacturers Association (PMA) (Ref. 68), merits special attention because it purports to demonstrate that PPI's about drugs have almost no effect in improving knowledge or compliance. After careful review of this analysis, FDA has concluded that the methodology was flawed and should not be relied upon with regard to the effects of written drug information on compliance. The details of the study and FDA's analysis of its methodology follow.

In 1983, PMA funded a grant to assess the literature regarding mechanisms for improving patients' knowledge and use of prescription drugs. The authors performed a meta-analysis of studies selected from the patient education/compliance literature. They examined eight different strategies to improve patient knowledge and use of prescription drugs: Counseling, group education, behavior modification, counseling plus materials, materials alone, memory aids, counseling plus memory aids, and PPI's. The authors concluded that seven of the strategies improved patient knowledge and use by 24 percent to 72 percent; however, PPI's had practically no effect in improving patient knowledge or compliance. They concluded that PPI's were an ineffective tool to improve patients' knowledge about or use of medication.

FDA staff reviewed the meta-analysis and found its conclusions to be unsupported by the analysis performed by its authors. There are major definitional and methodological problems with the authors' analysis.

First, the inclusion criteria used were not rigorously followed. Following Kanouse, et al. (Ref. 69), the authors of the meta-analysis defined PPI's as ''standardized leaflets which accompany a prescription drug as it is dispensed to the patient and which are designed to inform patients about a drug's actions, indications, and proper use, and to alert them about risks, necessary precautions, and possible side effects.'' However, as a practical matter, the authors sorted studies meeting this definition into two analytical groups (''materials'' and ''PPI's''). They placed studies in the PPI category if the authors of that study called the leaflets ''PPI's'' as opposed to ''written'' information. The ''materials'' group included studies that did not designate the written materials as PPI's.

Second, the PMA authors used a different analytical procedure for the PPI section of their analysis than for the remaining sections. Selecting test and control groups for the meta-analysis is a vital aspect of this type of analysis because it seeks to estimate the effect size of the difference between these groups. For all but a few studies examined in the meta-analysis, a group of subjects that received an intervention (e.g., counseling) was compared to a group that did not receive the intervention (e.g., no counseling). However, for the PPI analysis in 27 of the 28 studies examined, the test group was compared to a group that received an alternative version of that PPI. Thus, for PPI's, the authors compared intervention to intervention rather than intervention to control.

The 27 PPI studies included in the meta-analysis were from FDA-funded studies that had been conducted by the Rand Corp. These Rand studies examined 12 different formats for communicating information to patients for each of three drugs: erythromycin (an antibiotic), flurazepam (a sleeping pill), and estrogens (for postmenopausal symptoms). The Rand studies included no-intervention control groups for erythromycin and flurazepam. For estrogens, the Rand study included a control group composed of patients receiving the FDA-approved PPI for estrogens. Citing incompatibility of the data offered by Rand with meta-analytical procedures, the authors of the PMA-funded study selected the intervention group that they believed should have performed worst (i.e., was less sound educationally) to serve as the control group.

The authors of the Rand studies concluded that PPI's lead to reliable gains in drug knowledge. This conclusion directly contradicts the PMA meta-analysis conclusion that was based primarily on Rand study results. The Rand studies were designed only to compare the effects of variations in style of information presentation within PPI's. Each of the PPI's studied by Rand

was highly similar in content and varied only in format or style. Therefore, the selection of one of the intervention groups to serve as a control by PMA researchers was inappropriate and obfuscated differences Rand researchers observed and reported.

IV. Patient Education Programs Instituted Since 1982

A. NCPIE's Coordinating Function

As described in FDA's final rule that revoked mandated PPI's (47 FR 39147), the major coordinating body for private sector organizations has been NCPIE. NCPIE is a voluntary organization comprised of approximately 370 member organizations representing health care professionals, consumer groups, voluntary health organizations, pharmaceutical manufacturers, Government agencies, and other health-related groups. Since its inception in 1982, NCPIE has engaged in numerous activities to improve the delivery of communication of prescription drug information to patients and consumers. For example, NCPIE has coordinated broad scale public service advertising campaigns targeted at improving medication use among older Americans and children, sponsors an annual national conference on prescription medicine information and education, has targeted reports on drug use in population segments (elderly, pediatric, women), sponsors ''Talk About Prescriptions Month'' every October, and creates and distributes educational materials such as the ''Brown Bag Review Kit,'' in support of the National Brown Bag Medicine Review Program, which NCPIE developed with support from the Administration on Aging. NCPIE has also compiled a directory of drug information, citing numerous patient education resources. These include drug leaflet programs; specialized pamphlets, newsletters, etc., which are directed to improving use of specific drugs; books for patients and health professionals; high-tech or other automated videos, telephone, and computer software; interactive-computer kiosks, and other audiovisual instructional aids; compliance reminder systems, aids, and devices; program guides to set up educational systems; and other patient information and education systems.

B. Pharmaceutical Industry Programs

In the past decade, the pharmaceutical industry has developed and distributed drug information to consumers, both directly and through health professionals.

In the early 1980's, these programs provided health professionals with leaflets or booklets describing various disease processes and medications that might be used to treat these conditions (Ref. 20). In recent years, the industry has begun to prepare numerous additional materials, ranging from simple brochures to elaborate patient education kits and programs. Currently, the great majority of pharmaceutical products prescribed to patients have some patient materials developed as well.

Recently, pharmaceutical companies have begun the development of relatively comprehensive patient support programs. Several such programs have been developed, including the following: Alliance Program, Good Start Program, Patient Support Program, Wellspring Service, Partners Program, Growing with Humatrope, The Patient at Heart, Stay in Control, HealthQuest, Unique Patient Support Program, Clinical Experience Program, CardiSense, Hands on Health, Seasons, Care Kits, Asthma Management Program, Total Lifestyle Connection, and Dialogue. These programs provide a consistent flow of information to patients initiated on therapy for the target drugs. They provide information about the product as well as information about the disease and lifestyle modifications necessary for treatment. As promotional labeling or advertising, these materials necessitate the inclusion of labeling information and must meet other regulatory standards.

In the mid-1980's, the pharmaceutical industry began to direct advertisements to the consumer to promote certain prescription drugs. These advertisements have taken many different forms. ''Help-seeking'' advertisements encourage consumers to seek professional assistance for certain conditions, but do not promote a particular product. Reminder advertisements merely mention a product and its dosage form but give no other suggestions or representations of how the product is to be used or its benefits. Institutional advertisements describe the pharmaceutical company and the work it is doing.

There has also been a significant increase in consumer-directed advertisements that directly promote a prescription drug product or group of products and discuss in detail product risks and benefits. Direct-to-consumer advertising (DTCA) has been placed in consumer magazines or newspapers for several products, including Actigall, Cardizem CD, Claritin, Cognex, Estraderm, Felbatol, Habitrol, Hismanal, Mevacor, Minitran, N.E.E. 1/35, Neurontin, Nicoderm, Nicorette, Nicotrol, Norplant System, Ortho Novum 777, Premarin, Proscar, Prostep, Rogaine, Seldane and Seldane-D, and Transderm Scōp. FDA reviews DTCA for these products to ensure that they are not false or misleading and are in fair balance. However, FDA acknowledges that the rules that govern the regulation of advertising focus primarily on advertising geared towards health professionals.

Although individual advertising materials disseminated to consumers may meet regulatory standards in that they are in fair balance and are not false or misleading, FDA remains concerned that the overall practice of DTCA will have cumulative effects of providing patients with information based primarily on promotional materials furnished by the pharmaceutical industry, and that this promotional focus will result in problematic overall perceptions of prescription drugs. For example, it would not benefit the public health for consumers to perceive prescription drugs—i.e., potentially dangerous medicines—as relatively nonserious, or for consumers to believe that nonprofessionals are competent to make skilled therapeutic decisions. FDA believes that the availability of quality patient information will help to counter any unbalanced perceptions of prescription drugs promoted to the consumer.

C. Patient Information Supplier Programs

During the past 10 years, numerous health professional and consumer associations and private sector organizations have initiated programs to educate drug consumers about their prescriptions. FDA has worked to support these programs through staff support, expert review, and evaluating research.

1. Major Associn Programs

a. *AMA.* In 1982, the AMA initiated a program to encourage licensed practitioner distribution of written patient medication information (PMI's). AMA's PMI sheets were designed to provide licensed practitioners with written drug information they could give to a patient at the time a medication is prescribed. Each PMI consists of a single sheet of paper, printed on both sides, containing information about the specific drug or drug class. The instructions are designed to improve the effectiveness of drug therapy, to reduce the risk of adverse drug reactions, and to reinforce communication between patient and licensed practitioner. Specific PMI's are

based on the drug information leaflets produced by the USP, which are revised to conform to the PMI format and are then subjected to additional review by the AMA and other medical consultants. Currently, there are 101 drug titles, including classes and individual drugs, offered through the PMI program. This provides coverage of over 1,700 of the most widely prescribed drugs.

Available sales data indicated a recent downturn in the use of PMI's. While over 84,000 pads (each consisting of 50 sheets) were sold between July 1, 1987, and June 30, 1988, a steady annual decline in unit sales resulted in a sales figure of approximately 47,500 the 1993 fiscal year.

b. *AARP pharmacy service.* The AARP Pharmacy Service program, Medication Information Leaflets for Seniors (MILS), addresses the special drug information needs of the elderly. AARP requires its pharmacies to include the drug information leaflets with the original and first refill mail-order prescription for each patient. AARP designed the leaflets in consultation with FDA and geriatric experts. The leaflets cover between 80 percent and 85 percent of all drugs dispensed by AARP pharmacies.

In addition to its printed materials, AARP also conducts seminars concerning the safe and effective use of prescription and over-the-counter drugs, and the special health care needs of the elderly. For example, AARP advises its members how to prepare for an office visit, what information to share with the licensed practitioner and pharmacist, what information to get about each drug prescribed, and how to organize a system for taking medicines.

c. *Other association programs.* Several other voluntary health organizations have been involved in the development and delivery of health information to patients. These programs are described in the NCPIE Directory (Ref. 18). Some of the organizations that have developed programs include:

(1) American Association of Family Physicians (AAFP): the DUET program (recently discontinued program providing abstracts for photocopying and distribution);

(2) American Dental Association: DDIS (Dental Drug Information Series)—distribute leaflets;

(3) American Academy of Pediatrics: Patient Medication Instruction Sheets—distribute leaflets;

(4) American Society of Health-Systems Pharmacists: Several programs, such as MEDTEACH—software program, Medication Teaching Manual—book, Drug Information Service—health professional reference book.

2. Selected Private Sector Programs

In addition to these associations, several private sector information suppliers have developed programs to communicate drug information to the patient, including the following.

a. *USP.* USP has developed a drug information data base and prepares written information. Both the data base and prepared medication leaflets are used in many patient information programs. For example, USP distributes drug information leaflets, which can be personalized for the organization, to State pharmaceutical associations, chain and independent pharmacies, and large institutions.

USP also produces the ''USP Dispensing Information, Advice for the Patient'' publication as part of its 3-volume ''USP Dispensing Information'' (USP DI) series. The ''Advice for the Patient'' publication contains monographs that provide general information (such as information that the patient should tell his or her licensed practitioner, nurse, or pharmacist before using the drug product, proper use of the drug product, storage conditions, precautions, and adverse reactions) about drug products. These monographs form the basis of the USP's Patient Drug Education Leaflet program and other programs, such as the National Association of Retail Druggists' (NARD) Patient Information Leaflet program. USP DI Patient Education Leaflets are currently available from USP as preprinted, English-language leaflets for the 88 drugs or families of drugs most frequently used in ambulatory care. USP also publishes full text, easy-to-read leaflets. In addition, abstracts from the USP DI are available to health care providers who wish to institute their own patient education leaflet programs. These abstracts are stored on a data base, may be personalized for the health care provider, and are available in both English and Spanish.

b. *Medi-Span, Inc.* Medi-Span, Inc., has developed a drug education data base consisting of patient-oriented information about prescription and OTC medications. Drug information is both product and dosage form specific. Programming by the user or computer software vendor and integration into the pharmacy, medical records or patient care software package allows health professionals to print a customized counseling sheet for the particular drug product.

Medi-Span, Inc., also produces a stand-alone MS–DOS software version of their patient drug information which allows printing of a customized patient counseling message for prescription and OTC medications. This software does not require programming by a software vendor and is marketed to home health care agencies, retail pharmacies, consultant pharmacists, physician offices, drug information centers, and small hospital pharmacies. The software allows for selected sections of the product information to be printed.

D. Continuing FDA Encouragement

Since the withdrawal of the PPI regulations, every FDA Commissioner and HHS Secretary has urged private sector health professionals to be more active in counseling patients about their medications. In 1992, Commissioner Kessler and several other senior FDA staff renewed this call for private sector health professional medication counseling, reinforced by the provision of written information. Professional journals published several articles publicizing FDA's renewed interest in increasing the provision of written information to patients (Refs. 92 and 93). In addition, several speeches were delivered to communicate similar messages. For example:

(1) On March 16, 1992, at the Opening General Session of the Annual Meeting of the American Pharmaceutical Association (APhA), the Commissioner challenged pharmacists to renew their commitment to patient education. After taking note of the House of Delegates' newly adopted position that ''makes pharmacists responsible for initiating pharmacist-patient dialogue,'' the Commissioner reviewed the benefits of patient information and the key role pharmacists play as gatekeepers.

(2) In his address in June of 1992 at the Biannual Meeting of the American Nurses Association, the Commissioner asserted that patients are eager to learn more about medications they are taking and that nurses should step up their efforts to instruct patients on how to take their medications properly.

(3) At the National Association of Chain Drug Stores (NACDS) Pharmacy Conference in the summer of 1992, the Commissioner emphasized that pharmacists are ideally suited to take the lead in the patient education effort because of their training and unique position in the health care system. He also stated that it is inconceivable that a patient could leave the pharmacy with a new prescription medication and not have written advice about how to get the maximum benefit from their medication.

(4) At the USP Open Conference on Patient Education in September 1992,

the Deputy Commissioner for External Affairs stated that in order to make patient education more effective, all health professionals need to become more involved and invested in the process. She stated that the question should no longer be ''Should I counsel?'' but ''What should I say?''

(5) In May 1993, at the NCPIE Annual Conference, the Deputy Commissioner for External Affairs once again challenged health professionals to do a better job of communicating with patients. She also predicted that the patient education message would become more critical as we approve drugs with much more complex risk/benefit profiles. Further, she stated that patients must understand the risks and limitations of the products so that they can use the drugs properly.

In addition, professional staff from FDA's Office of Health Affairs, Office of Consumer Affairs, Office of Policy, and the Center for Drug Evaluation and Research have researched and analyzed patient information and challenged pharmacists, physicians, and nurses to renew their commitment to patient education. At the same time, through speeches, participation at professional meetings, site visits, and articles in professional journals, these agency staff have renewed and amplified the agency effort to promote communication to patients about their medications.

V. Evaluation of Progress

As mentioned earlier, in the revocation of the 1980 mandatory PPI regulation, FDA indicated that it would be conducting surveys to evaluate the availability of adequate patient information. This section discusses FDA surveys and other available data that assess the effectiveness of the private sector initiatives in providing patient medication information.

A. FDA Surveys of Oral and Written Patient Information

FDA sponsored national telephone surveys of patient receipt of information about new prescriptions in 1982, 1984, and 1992 (Refs. 22, 23, and 24, respectively). In each survey year, researchers collected data from approximately 1,000 patients who had received a new prescription for either themselves or a family member during the 4 weeks before the interview. Researchers asked respondents about their experiences at the licensed practitioner's office and the pharmacy, and whether they had gained any drug knowledge independent of those experiences. In an effort to establish patient drug education trends, the latter report (Ref. 24) compares data collected from the surveys over the past 10 years.

1. Experiences at the Licensed Practitioner's Office

a. *Oral counseling.* When asked whether they received any prescription drug counseling at the licensed practitioner's office, approximately 66 percent of patients in each year answered affirmatively. The surveys asked patients about five specific drug counseling topics: (1) Directions regarding how much medication to take, (2) directions regarding how often to take the medication, (3) information about refills, (4) precautions, and (5) adverse reaction information. Researchers found no meaningful change in the percentage of patients whose licensed practitioner voluntarily instructed them how much or how often to take their medication. Slightly over half of the respondents in each year received instructions without questioning their licensed practitioner. Researchers discovered a small gain in counseling about precautionary information, from 26 percent in 1982 to 33 percent in 1984; the level remained at 33 percent with no increase experienced between 1984 and 1992. For counseling about adverse reactions, the rate measured increased from 23 percent (in 1982 and 1984) to 29 percent in 1992. Less than 5 percent of respondents, in each of the three surveys, received any additional counseling other than directions for use, refills, precautionary and adverse reaction information.

The rate at which patients question their licensed practitioners about their prescriptions has also remained low over the past 10 years; only between 2 percent and 3 percent ask for directions regarding the correct use of their prescriptions and 4 percent to 6 percent ask for refill, precaution, and adverse reaction information. When researchers examined both spontaneous counseling and spontaneous questioning, the only meaningful gain in licensed practitioner-patient communication was in the area of adverse drug reaction counseling. However, even though this rate increased from 27 percent to 35 percent, only slightly more than one-third of patients receive any counseling regarding possible adverse drug reactions.

b. *Written information.* A comparison of the three surveys reveals an increase in licensed practitioner dissemination of written drug information, from 5 percent in 1982, to 9 percent in 1984, to 14 percent in 1992. Seventy-five percent of the 1992 respondents who received written information said that they received an instruction sheet, 55 percent of which were preprinted, and 39 percent of which were printed at the licensed practitioner's office. Overall, approximately 5 percent of all participants in the 1992 survey received a personalized, computer-generated brochure or sheet to instruct them about their prescription medications.

2. Experiences at the Pharmacy

a. *Oral counseling.* During the past 10 years, fewer pharmacists, and more pharmacy clerks or cashiers, are distributing prescriptions to patients at the pharmacy counter. In 1992, 43 percent of consumers received their prescription from the pharmacist, and 41 percent received their prescription from a clerk. However, even though the number of pharmacists distributing drugs to consumers has decreased, the amount of counseling has increased.

Respondents were questioned about the same five areas of counseling at the licensed practitioners' office. There has been an increase in pharmacist counseling in four out of the five prescription education areas that were tested. In 1992, 32 percent of the patients said that their pharmacist instructed them about how much or how often to take their medicine, as compared to between 20 percent and 23 percent in 1982 and 1984. Similarly, there was an increase in refill and precautionary counseling. The rate for refills increased from 12 percent in 1982 to 18 percent in 1992, and for precautions from 8 percent in 1982 to 21 percent in 1992. Adverse drug reaction counseling decreased in 1984 to 9 percent, from 16 percent in 1982. It has increased since 1984, to 13 percent, but remains below the 1982 level.

Although research indicated gains in pharmacist counseling in four of five areas covered, analysis of the percentage of patients who obtain counseling about any of the topics covered indicates that this percentage has remained stable over the years. This suggests that patients obtaining counseling at the pharmacy are more likely to obtain a broader overview of topic coverage.

The percentage of patients who question their pharmacists has increased from 2 percent in 1982 to 5 percent in 1984 to the 7 percent to 9 percent range in 1992. The largest gain was made in the area of patients questioning their pharmacists about adverse drug reactions.

Data indicate that the type of verbal information that pharmacists are most likely to give reinforces the licensed practitioner's instructions on how often and how much medicine to take. In other words, although the data indicate

an increase in pharmacist counseling, patients are receiving redundant information. On the other hand, the increase in patient-initiated questioning resulted in patients receiving information at the pharmacy that they had not received at the licensed practitioner's office.

b. *Written information.* Respondents were asked if they received any written information furnished with the medicines aside from the label information on the medication container. The percentage of respondents answering affirmatively has increased over the three surveys. Specifically, 32 percent of patients reported receiving written drug information in 1992 as compared to 26 percent in 1984 and 16 percent in 1982. The type of additional information ranged from sticker labels affixed to the container to brochures and information sheets. Examining the particular form of information provided in the 1992 survey indicated that, overall, 23 percent of subjects reported receiving informational brochures or instructions (more than brief sticker labels).

FDA's 1992 survey also revealed changes in how written material is prepared. Technological advances, most notably in the use of personal computers, led to an increase in the dissemination of computer-generated information. Overall, 12 percent of patients in the 1992 survey received a computer-generated information sheet at the pharmacy.

3. Ten-Year Trends in Information Distribution

The data from these surveys do not indicate any sweeping changes in the nature or frequency of information disseminated either by licensed practitioner or pharmacist. However, the data do indicate some discernible trends.

Consumers are more likely to receive oral instructions for use and information about precautions and adverse reactions related to their medicines today than they were 10 years ago. In addition, patients are more likely to receive some form of written prescription information today, especially at the pharmacy, than they were 10 years ago. There have been some gains in all categories of information disseminated at the pharmacy, except adverse reaction information. However, a broader analysis indicates that the gains made in patient counseling are attributable to an increase in the number of categories of information disseminated, not to an increase in the number of patients who receive counseling. Finally, despite overall gains in health professionals' counseling and disseminating written information, over three-fourths of all patients in the 1992 survey received no substantial written prescription information. Further, data from the 1992 survey indicate that when a drug is initially prescribed and dispensed, approximately half of all patients receive no forewarning of possible adverse reactions that they may experience from their medications.

B. Other Literature About Oral and Written Patient Information

1. Patients Continue to Want Written Information

In the 1979 PPI proposal, FDA reviewed five studies in which consumers were asked about their desire to obtain additional information about their prescriptions. Three of the studies specifically addressed patients' desire to obtain printed information about their medication. The studies indicated that the majority of patients who were provided written information with their medication (oral contraceptive users or those in an experimental test of a PPI for Thiazide drugs) wanted to obtain written information for additional drugs (86 percent to 97 percent wanted this additional information). The third study simply asked consumers if they thought it was important for printed patient information to be provided with prescription drugs. Sixty-four percent responded affirmatively.

Studies completed after 1979 continue to support the previous trends that indicate that patients want to know more about their medications, especially the risks, and that people would like to receive written information with their prescriptions. A 1982 AARP survey of people over age 45 indicated that 60 percent of respondents would like to receive written information with their medication. The majority of respondents indicated that their licensed practitioner or pharmacist did not provide written information.

A national survey conducted in 1984 by the Columbia Broadcasting System also indicated that labels on medication and inserts would be useful for obtaining information about safety and potential adverse reactions (83 percent and 74 percent) as well as effectiveness (60 percent and 64 percent) (Ref. 25). Subjects in the survey were asked to rate 27 categories of information about medication in terms of their perceived knowledge about that category and how important it would be to know about that aspect of information. The perceived knowledge gap (i.e., the difference between ratings of knowledge and perceived importance) for safety and efficacy of medication was 50 percent (i.e., 27 percent of the sample believed that they were well-informed about the safety and efficacy of medications and 77 percent believed that it was important to be well-informed about this aspect of medication information).

Another study, conducted by the President's Commission for the Study of Ethics in Medicine and Biomedical and Behavioral Research (Ref. 26), found that both licensed practitioners and members of the public believed that patients should be informed about the potential adverse reactions of medical treatment. The survey also indicated that patients and licensed practitioners alike believed that this information should be delivered spontaneously, without patients having to ask for the information. The majority of the general population surveyed (64 percent) also asserted that they should be informed of serious risks regardless of how likely the risk was to occur.

Other studies, both in this country and abroad, consistently show that patients want more information about their drugs (Refs. 29, 38, 42, and 43), including information about precautions and interactions (Ref. 33). In one study, when asked whether they want information orally, in writing, or both, more patients preferred to have both (45 percent) than preferred only written information (21 percent) or only oral information (30 percent) (Ref. 43).

2. Limitations of Current Patient Counseling Efforts

The literature since 1982 demonstrates that patients need and want additional information about their medications. Studies have shown that licensed practitioners and pharmacists often do not provide information about drugs to patients (Refs. 27, 28, and 29), including information about side effects (Refs. 29 through 32), precautions, and interactions (Ref. 33).

A study published in 1987 revealed that, while over 90 percent of the patients interviewed had received some information about their drug treatment from licensed practitioners, nurses, or pharmacists, only 32 percent received counseling regarding adverse reactions (Ref. 29), even though another study showed that patients rate information about precautions, drug interactions, and adverse reactions as most important (Ref. 33). Only 14 percent of patients in the 1987 study received written information, despite the fact that 74 percent said that written instructions would be valuable. Despite the great demand for information, however, only one-third of the patients in this study

questioned their licensed practitioners about their treatment (Ref. 29).

Two FDA-sponsored studies, one of consumers and one of physicians and pharmacists, reveal that the professional and consumer groups have substantially different perceptions of the type and amount of information provided by licensed practitioners, as well as the intensity of patients' demand for drug information. Eighty-eight percent of licensed practitioners surveyed believed their patients were well or adequately informed about the purpose and use of their prescriptions. However, patients revealed that only 26 percent received oral information about side effects from licensed practitioners' offices (11 percent from pharmacies) and only 32 percent of patients reported receiving oral precaution information from licensed practitioners' offices (16 percent from pharmacies). Approximately 60 percent received information about how and when to take the medications from licensed practitioners and about 25 percent from pharmacists (Ref. 34).

Licensed practitioners may find it difficult to counsel patients because they are not comfortable in the role of counselor (Ref. 32) or because medical records do not always contain the information necessary for them to provide appropriate counseling for individual patients (Ref. 35). For example, a study that monitored charts of patients who had been prescribed amiodarone found that only 14 percent of the charts documented patient education concerning photosensitivity which can be controlled, at least partially, with a sunscreen (Ref. 31). In another study, researchers reviewed the charts of hospital patients who had been prescribed benzodiazepines. Fifty-seven percent of the charts failed to show whether the patient used alcohol, even though the introduction of alcohol could result in a life-threatening interaction (Ref. 35).

When licensed practitioners do provide counseling, information on side effects is often omitted (Ref. 29), and side effect information, if given, usually relates to the most frequent, rather than the most serious, side effects (Ref. 30).

Even if counseling is provided, patients may not remember the information that is given. In a review of primarily pre-1983 research on this issue, one author notes that it is well established that patients forget much of what they are told during medical consultations (Ref. 36).

Pharmacists, as well as licensed practitioners, often fail to provide information about medications. In a 1993 nationwide survey of 2,000 consumers, a substantial proportion of respondents stated that their pharmacists did not regularly tell them how to take their medications or advise them of possible adverse reactions (Ref. 37). Almost half of the consumers said they were not told how to take their medicine. Almost 30 percent reported that their pharmacist never warns them of common adverse reactions that are bothersome although not necessarily serious. Nearly half of the consumers responded that their pharmacist never told them about serious adverse reactions for which they should contact their licensed practitioner. The author of this study notes that these results conflict with a survey of pharmacists, conducted by two pharmacist associations, in which 89 to 98 percent of pharmacists reported that they orally counsel their patients (Ref. 37). The disparity between these two surveys may suggest that pharmacists and consumers have different perceptions about the quality and quantity of counseling provided by pharmacists. The results of a 1992 Wisconsin Statewide survey of pharmacy patients are consistent with the nationwide consumer survey. In this study of persons who recalled the time their last new prescription was filled, 53 percent had not received any oral consultation from their pharmacists, and 23 percent had not received consultation from their prescribers. Nineteen percent received no consultation from either pharmacists or prescribers. For new and refill prescriptions combined, 60 percent reported receiving no oral information from pharmacists and 26 percent reported none from prescribers. The authors cited comparable findings in other studies (Ref. 27).

These results are similar to responses given in a 1985 survey, in which pharmacists reported having provided oral counseling for 52 percent of patients with new prescriptions and for 18 percent of those with refill prescriptions. The authors concluded that pharmacists provide oral and written information selectively to patients and this information is usually not complete. They suggest increased counseling and the provision of comprehensive leaflets about the medication (Ref. 28).

3. Elderly Patients Have Special Information Needs

In a review of the literature, one author demonstrates that elderly patients, who are prone to forget or to be confused, and who may be taking several medications, require special attention when drug information is given (Ref. 38). Research indicates that 23 percent of nursing home admissions are attributable to noncompliance with drug therapy, in part because a gap exists in elderly patients' understanding of proper medication use (Ref. 4). They frequently do not remember to take their medications and report receiving little information about their medications (Ref. 41). One study concluded that, because almost 75 percent of elderly patients could not remember receiving oral instructions regarding potential adverse reactions, and only 14 percent claimed to have received any written information, the elderly require special medication education that includes both oral counseling and written reinforcement (Ref. 52).

C. The Adequacy of Currently Available Written Information

Patients report reading written information when they receive it (Ref. 38). However, currently available written material often is inadequate. Even when written information is provided to patients, the material may not be expressed appropriately to communicate the important information (Ref. 39), and patients often fail to understand the written materials (Refs. 38 and 40). In addition, written materials often take the form of auxiliary labels (Ref. 28) that offer a few directives with no explanation or background information to improve comprehension and retrieval of the message.

However, with the trend in pharmacy toward computer automation of label-making and record keeping, there has also been an increase in electronically-available patient drug information designed to be given out with dispensed prescriptions. FDA reviewed patient drug information from eight independent sources that provide information on electronic media designed to be used by retail pharmacists as an aid to patient counseling at the time of drug dispensing. These sources were the American Society of Health-Systems Pharmacists, Clinical Reference Systems, Ltd., Facts and Comparisons, First Data Bank, Medi-Span, Inc., Medi*CHEX, Inc., Pharmex, and the U.S. Pharmacopeia. The accuracy and comprehensiveness of the patient information for three drugs was determined by an assessment of consistency with the approved labeling. The specificity of the information communicated was judged on the basis of whether the directions for use were clear and whether the risk information conveyed the significance of the risk, how to recognize negative

consequences, and the proper response to take should they occur.

Patient information was gathered from each source for three drugs: Oral alprazolam (a benzodiazepine), oral amoxicillin (a penicillin), and oral enalapril (an angiotensin converting enzyme (ACE) inhibitor). Only four of the eight sources produced drug-specific information for the three drugs chosen; the other four sources produced therapeutic class information.

FDA's review found substantial differences between sources in the quality of information provided. One source included no mention of indication for any of the three drugs studied. Only two of the eight sources mentioned both of alprazolam's approved indications (i.e., anxiety disorder and panic disorder). On the other hand, the sources that provided general benzodiazepine information mentioned uses that are not approved for alprazolam, including the treatment of insomnia, muscle spasm, convulsive disorders, and symptoms of alcohol withdrawal.

Only two of eight sources mentioned either of alprazolam's contraindications (i.e., known sensitivity to a benzodiazepine or acute narrow angle glaucoma). Side effect/risk information tended to be highly general and nonspecific; the significance of the risks was often minimized and the serious, but rare risks were often missing. For alprazolam, all information providers included the common side effects of drowsiness and dizziness, but four failed to mention any risk incurred when alprazolam is taken during pregnancy and none of them described the risk itself (either a birth defect when taken during the first trimester or withdrawal symptoms in the child at birth). Unlabeled side effect information (''wormlike movements, tongue protrusions, chewing motions, and lip smacking'') were reported for alprazolam by some sources; none of these effects appear in its label.

Only two of the eight sources mentioned amoxicillin's only contraindication (previous allergic reaction to any of the penicillins). Only two of the eight warned the patient to be aware of symptoms that may signal a superinfection with mycotic or bacterial pathogens.

None of the eight sources mentioned the contraindications for the use of enalapril, i.e., allergic reactions or swelling (angioedema) on previous treatment with similar drugs. Two of the sources failed to warn the patient about symptoms of angioedema, a potentially deadly allergic reaction. Of the six including such symptoms (i.e., swelling of face, extremities, eyes, lips, tongue or difficulty in swallowing or breathing), only one advised the patient experiencing such symptoms to take no more drug and to seek medical attention immediately.

The analysis did not assess the accuracy of important and relevant information not derived from the approved labeling. The most common types of such information were: (1) Directions for what to do in case of a missed dose, (2) proper storage conditions, (3) directions for what to do in case of accidental ingestion or overdose, (4) directions for when to take the drug with respect to meal times. However, there was little consistency between sources in inclusion of this information. For example, different sources gave opposing directions for handling missed doses and for when to take the product in relation to mealtimes.

The lack of specificity and contextual information found in information from some of these systems is of special concern. Research examining the effectiveness of warning labels points to the need for warning messages to include sufficient context to explain to users why they should take certain actions or precautions or pay attention to certain aspects of the product. Standards for warning labels indicate that, in addition to being conspicuous and understandable to the targeted population, labels need to get the reader's attention (e.g., by use of a signal word), and disclose the potential danger, why it is important to avoid the danger, and specific instructions regarding how to avoid it.

Research on warnings provided in consumer-directed advertisements for prescription drugs indicate that general warnings (e.g., see your doctor) do not give consumers a sufficient understanding of the risks inherent in product use. Consumers interpret advice to consult a health care professional as ''general reassurance'' that the condition is under sufficient treatment, rather than that ''specific vigilance'' is needed to protect the consumer from product risks (Ref. 94). Therefore, nonspecific advice to consult with the health care professional may be insufficient as a means of communicating risk information.

Searches through a frequently-used patient medication information data base for products with boxed warnings in the approved labeling (generally indicating an extremely serious warning) revealed a general lack of the kind of information that would allow the reader to understand the reason for or significance of the warning. For example, despite Hismanal's boxed warning concerning life-threatening heart arrhythmias that may occur on use with common prescription antibiotics and antifungals, the advice given was simply to check with the doctor or pharmacist before taking any new medicine, either prescription or over-the-counter. The information for Seldane-D, which has the same boxed warning, added the names of the drugs that cause the interactions. Neither specified that a potential outcome of mixing these drugs is a fatal heart attack.

D. Recent Changes in Pharmacy Provision of Patient Information

The most recently analyzed FDA survey of patient receipt of medication information was conducted at the end of 1992, immediately prior to the implementation date of the 1990 Omnibus Budget Reconciliation Act (OBRA '90) (Ref. 70). OBRA '90 requires pharmacists to offer to counsel Medicaid recipients. Guidelines and requirements for how to implement this statute have been issued by individual states. Many states expanded the covered population to include all patients. In addition, several pharmacy organizations, individual pharmacies, and drug store chains have been implementing their own policy regarding prescription drug counseling.

In recent meetings, FDA staff informally discussed the issue of patient education with representatives from consumer, medical professional, pharmacy, pharmaceutical industry, and patient information provider groups, including the National Consumer League, AARP, NCPIE, AMA, AAFP, ASHP, APhA, NARD, NACDS, Pharmaceutical Research and Manufacturers Association (PhRMA), USP, and Medi-Span. In many of these discussions, representatives suggested that the implementation of OBRA '90, although focused on oral counseling, had also significantly affected the distribution of written information.

Several of these groups also recently conducted surveys to describe pharmacist behavior and perceptions concerning printed patient information. According to a 1993 NARD survey of its members, 92 percent of independent retail pharmacists responding to the survey reported that they provide printed patient drug information. NACDS determined that 95 percent of responding drug store chains reported having a printed patient information program in place in 1994.

However, these estimates do not allow specification of the type of printed patient information available.

Manufacturer-supplied promotional brochures, as well as leaflets that accompany drug products in unit-of-use packaging (e.g., oral contraceptive patient labeling) and short labels designed to stick onto prescription vials would be included in the broad definition of printed patient information. These surveys were not designed to examine these distinctions.

The Research Institute of Pharmaceutical Sciences of the University of Mississippi School of Pharmacy conducted surveys of chain and independent drug stores in the spring of 1994. In one survey, 77 percent of the pharmacy manager respondents reported using printed patient information supplied by commercial vendors; 64 percent reported using printed patient information from pharmaceutical manufacturers; and 17 percent reported using printed patient information from nonprofit associations. In a separate survey, 93 percent of responding community pharmacists indicated that they used printed patient information. However, only 54 percent of pharmacists indicated that they give out printed patient information with at least 75 percent of all new prescriptions dispensed, and only 37 percent give out printed patient information with at least 95 percent of all new prescriptions dispensed. Sixty-eight percent of the pharmacists indicated that computerized patient information was available in their pharmacy. However, on average, the computerized patient information was reported being accessed for patient counseling purposes an average of 86 times per week. In contrast, the average number of prescriptions dispensed per day was 131, suggesting that, even though available, patient information systems are not being fully utilized.

However, there is preliminary evidence that the rates of prescription drug information received by patients has increased substantially in the past 2 years, based on comparison with the 32 percent of respondents in the 1992 FDA survey who reported receipt of any written information in addition to the label on the container, and the 23 percent who reported receiving ''longer'' information sheets and brochures (not including sticker labels). The new evidence comes from two recent patient surveys.

First, in July 1994, patients/caregivers who obtained a prescription from a pharmacy within the past 6 months were surveyed for the National Association of Boards of Pharmacy (Ref. 95). In this survey, 64 percent of respondents said that they received printed materials about their medication from the pharmacy. However, these data cannot be examined further as a function of how much of this percentage represents short ''sticker label'' information and how much represents ''longer'' information sheets and brochures. Second, a repeat of the FDA patient information survey was conducted in December 1994 and January 1995, with data collection cofunded by the Health Care Financing Administration. Preliminary data from this survey also support the occurrence of an increase in distribution of written information to patients; 58 percent of patients reported receiving some form of written information at the pharmacy. The rate of dissemination of ''longer'' information (more than sticker labels) was 55 percent.

VI. Relationship To International Activities

On March 31, 1992, the European Community (EC) adopted a Directive requiring its member States to refuse an application to place a medicinal product for human use on the market if the product's user package leaflet did not comply with the Directive (Ref. 71). The EC based its mandatory leaflet program on the desirability of uniform labeling among member countries and on consumer protection. The Directive states that the leaflets are necessary in order to ensure that medicinal products are used correctly on the basis of full and comprehensible information.

A user package leaflet must accompany all human drug products unless the manufacturer includes the required leaflet information on the outer or immediate packaging. The EC leaflet must include the following information:

(1) *Identification of the product*—Name of the product, active and excipient ingredients, and pharmaceutical form;

(2) *Therapeutic indications*—All therapeutic indications are to be listed unless the authorities find that the listing of certain indications would have serious disadvantages for the patient;

(3) *Information necessary before taking the product*— Contraindications, appropriate precautions for use, and special warnings, which must include categories for children, breast-feeding women, the elderly, and patients with special pathological conditions;

(4) *Instructions for proper use*—Dosage, method and frequency of administration, any limitations on duration of treatment, action to be taken in case of overdose, action to be taken in case of missed doses, and risk of withdrawal, if any;

(5) *Description of possible undesirable effects under ordinary use*—Including the action to be taken if the patient experiences an adverse reaction, with mandatory language directing the patient to contact his or her licensed practitioner if the patient experiences any effect not listed on the leaflet;

(6) *Expiration*—Including a warning not to use after expiration, instructions on proper storage, and description of visible signs of deterioration, if any; and

(7) *Last revision date of the leaflet.*

The user package leaflet may contain pictograms or symbols, but may not include language or symbols that the authorities regard as promotional. The language must be clear and understandable, the print must be clearly legible, and the leaflet must be offered in the official languages of the country where the product is placed on the market.

The Directive requires authorities to refuse a marketing application if the product's leaflet does not comply with the Directive. All changes to any contents of the leaflet that are covered by the Directive, except for information relating to the summary of characteristics, must be submitted to the authorities for approval. The authorities may exempt a drug product from the Directive if the product is not intended to be delivered to the patient for self-administration. Enforcement provisions allow the authorities to withdraw a medicinal product from the market until its leaflet complies with the Directive.

The Commission of the European Communities is directed to publish guidelines concerning:

(1) Special warnings for certain categories of medicinal products; (2) required information relating to self-medication; (3) legibility; (4) methods to identify and authenticate medicinal products; and (5) the list of excipients that must be featured on the labeling and the manner in which they must be indicated.

Countries were directed to take whatever measures necessary to comply with the Directive before January 1, 1993. The members were directed to implement the Directive after January 1, 1994. In other words, any application to place a medicinal product for human use on the market or to renew a marketing authorization after January 1, 1994, must include a user package leaflet that complies with the Directive.

Both the EC's leaflet program and FDA's proposed patient information program share the same patient education goal of increasing the safe and effective use of prescription drugs. Both patient information efforts should provide basic information about product

identification, directions for use, indications, adverse drug reactions, and precautions. Both programs also require that medication information for patients be written in understandable language, be devoid of promotional material, and be legibly printed. Both FDA and the EC recognize that the role of the printed leaflet is to reinforce the counseling that patients receive from health care professionals.

VII. Options Considered

FDA considered several alternative approaches that might remedy the problems associated with inadequate communication of prescription drug information to patients. From the literature reviewed, it was evident that a multifaceted, broad-based medication labeling and education program is needed that has as its central component the communication of information between health professionals and patients.

At a minimum, understandable information about medications should be supplied with new prescriptions for most products used without direct medical supervision. Written information should be designed to complement and reinforce oral counseling by prescribers and dispensers and achieve the overall objective of enhancing patient understanding and use of medications.

FDA examined a number of possible approaches in its consideration of how best to achieve the desired objectives of enhancing patient understanding and use of medications. After extensive deliberation and consultation with concerned consumer groups, pharmaceutical industry and pharmacy groups, and patient information suppliers, and careful consideration of the regulatory options, FDA determined that a combination of regulatory and voluntary efforts would take best advantage of available expertise and resources. Recent increases in pharmacy distribution of private-supplier patient medication information were strongly factored into FDA's analysis.

The remainder of this section describes the various alternative approaches considered, along with their advantages and disadvantages, in terms of how they address two components of such systems: the content of patient information and the distribution system involved. A major difference in the alternatives is the extent of FDA's role in determining the content of patient information. FDA's statutory obligation is to ensure that prescription drugs and biological products are labeled properly to encourage appropriate use. Traditionally, this has meant that FDA approves, on a word-by-word basis, labeling (i.e., package inserts) for prescription medications. This requires extensive resources for review and negotiation, and consequently would be associated with slower implementation. In contrast, deferral of the responsibility for reviewing content to private sector sources means that there is no assurance that patients would not receive inaccurate, incomplete, overly promotional or misleading information.

The alternatives also differ with regard to how patient information would be distributed. The last five approaches presented focus solely on the distribution of materials; they do not address content at all.

A. Continuation of the Status Quo

Should FDA decide to take no specific action, it would continue to require patient labeling only for carefully selected drugs. Production and distribution of patient information materials would depend primarily on the private sector.

This system has the advantage of allowing the self-correcting activities of an open marketplace to produce a wide variety of materials. Economic burdens are placed on manufacturers, health care providers, and dispensers only to the extent to which they wish to participate voluntarily or are compelled to do so because of other laws or regulations.

The disadvantage of this approach is that it has been in effect for over a decade and has not adequately improved the flow of information to patients. FDA has conducted and analyzed three surveys in the last decade to evaluate the degree to which the private sector has disseminated information to patients. Despite a variety of private sector programs and an increasing recognition that patients need and have a right to information about their medicines, a sizeable proportion of patients still receive no substantial written information. Further, initial evaluations indicate that written information currently disseminated varies widely in quality.

B. No Prior FDA Review

Under this option, the content of patient information would not be subject to prior review and approval by FDA. However, FDA would establish general requirements for this information. Under one form of this option, individuals preparing such information would be required to submit copies to FDA for review at the time of initial dissemination. Upon review, if FDA objected to any of the information, it would request that the information be revised to meet FDA requirements.

FDA would also require either that manufacturers supply dispensers with this information or that dispensers obtain or create such information and supply it to patients at the time of prescription dispensing.

This alternative has the advantage of an extremely rapid implementation period. Compliance with such a requirement would ensure that virtually all products would be covered within a very short period of time. If the system was imposed upon dispensers, the dispenser could easily choose a single system that would impose as small a regulatory burden as possible. Further, as multiple labeling systems would be developed, the dispenser would have the option of utilizing several systems simultaneously (selecting a different sheet for each product from among the differing systems) or selecting from among several systems to choose the best system to meet the needs of patients.

The major disadvantage of this approach was discussed above. Specifically, FDA's experience with the review of promotional materials issued by manufacturers (which utilizes a similar post-distributional review system), as well as its review of current patient information systems, suggests that considerable rewriting would be necessary to ensure consistency with professional labeling, nonpromotional tone, and lay language. This would also mean that patients might receive inadequate or misleading information until revisions could be effected. There would be considerable inefficiencies in the application of FDA resources because the same information would need to be reviewed for each of the systems submitted.

Despite these disadvantages, FDA has decided to propose a form of this general approach as the primary component of the selected option. It is discussed in more detail in section VIII. of this document.

C. FDA-Approved Patient Information

This approach defines both content and distributional requirements for Medication Guides, which would be FDA-approved patient information for most prescription drug products. Product sponsors would be required to prepare Medication Guides and to submit them to FDA for review and approval.

Prior FDA review of content has the advantage of ensuring that the information is consistent with information provided to health professionals, is nonpromotional, and is

written in lay language. A uniform format would allow patients to find needed information easily and increase their ability and willingness to use the information. Prior FDA review, however, has the disadvantage of taking a long time to implement because of limited resources. FDA has estimated that this approach would not be fully implemented for 10 years. In addition, mandated content does not allow for flexibility in the marketplace. For example, changes to content could not easily be made to account for changes in the state of knowledge about a product or the way in which it is customarily used.

Distribution of Medication Guides would also be required. Dispensers would be required to provide a Medication Guide to each patient receiving an applicable prescription drug. Manufacturers would be required to provide the dispenser with ''the means'' to ensure distribution. Distribution would be required with new prescriptions and on patient request when receiving a refill. Also considered, but rejected because of the associated major increase in distribution costs, was the option of requiring distribution with all (new and refill) prescriptions.

The advantage of this distribution system is that it would ensure that all patients receive written information about their medications. The disadvantage of this system is that drug dispensers, i.e., pharmacists, would need to store printed Medication Guides or generate computerized versions in the pharmacy. Even assuming that computer-generated Medication Guides quickly became the norm, it would take time to solve the logistical problem of integrating information from many different manufacturers into a system usable at the pharmacy level.

D. Distribution-Focused Approaches

These options do not address the content of patient information. They only describe different systems for distributing patient information.

1. Unit-of-Use Packaging

This approach would require that patient information be distributed in ''unit-of-use'' packaging. In this form of packaging, products are prepackaged in standardized amounts that can be dispensed directly to patients without the need for pharmacists to count out the specific number of tablets, capsules, etc., prescribed. The prescription label simply is applied to the unit-of-use package before dispensing to the patient. This type of packaging is currently used for certain prescription drug products dispensed in the United States (e.g., oral contraceptives, creams and lotions) and for most prescription drug products dispensed in Western Europe and in other parts of the world.

The advantage of unit-of-use packaging is that minimal time is needed for the dispenser to retrieve, verify, and dispense patient information. Except for packaging failures, prepackaging ensures that the patient will receive medication information with each product dispensed.

The disadvantage of unit-of-use packaging is that it requires more space for shipping and storing than other forms of packaging. Although the technology for unit-of-use packaging exists, it would be very costly for manufacturers to add unit-of-use packaging to already existing product lines. Wholesalers and retailers would need to increase space to store these products.

2. Reference Book At Dispensing Site

This distribution system would require that there be a looseleaf book located near where medications are dispensed. The book would contain a compilation of patient information leaflets, kept up-to-date by an individual at the site. Patients would be able to find the page(s) within the book that described their medication(s) and read the information during the time they were waiting for their prescription(s) or at any other time the book was not being used.

The advantage of this system is that it would reduce the burden on the dispenser of having to distribute a leaflet to each patient. Because the information would be read at the pharmacy, there would be a health professional present to answer any questions patients might have after reading the material.

There are several disadvantages of such a system. It does not provide patients with information that can be taken home for reading and rereading when patients were ready to take their medication. The system would not be viable for patients who do not pick up their own medication. Mail-order pharmacies would need to utilize alternative information systems. The system also requires patients to ''affirmatively seek,'' as opposed to ''passively receive,'' labeling information. Although this additional search process appears to be minimal, some patients would need help finding the particular pages where their medication was listed, space would need to be set aside in the pharmacy for such a book, and unless patients were guaranteed privacy, there could be considerable barriers to obtaining information for those concerned about this issue.

3. Interactive Computer Technology

Using available technology, computer systems could be placed in pharmacies or physicians' offices to allow patients to view patient information and print copies if desired. These ''information kiosks'' could also contain additional information, for example, suggestions for lifestyle changes or general information about how to use medications wisely.

The advantage of such a system is that only minimal direct input from the health professional would be needed. It would be available to anyone wishing to use it, and it could supply patients with additional information. The interactive technology allows the information to be focused on a particular patient's needs. The distribution system's location would also ensure that health professionals would be nearby to answer questions.

The disadvantage of this system is that not all patients would receive information about their prescribed medications. Only those patients with the time, skills, and assertiveness to seek out the information actively would benefit. This could be a particular problem for elderly patients who obtain a disproportionately high number of prescriptions, because they may be intimidated by computer technology.

4. Distributing a Book to Consumers

Under this distribution system, each household in the country would be provided a book of drug information. The book would be printed each year and mailed to each household or delivered to prescription dispensing sites where they could be obtained by a member of each household that requests a copy. The advantage of such a system is that it permits a once-a-year distribution of drug information, as opposed to the distribution on a continuous basis for each new prescription dispensed. It also provides patients with a convenient storage system for compiling patient information sheets.

The disadvantage of such a system is that it is extremely inefficient and costly. The book itself would be quite voluminous (the most conservative estimate is over 1,000 pages) and therefore costly to produce, distribute, and store. If provided without charge, one would expect consumers to be quite liberal in requesting copies, resulting in numerous copies within individual households; this would be both wasteful

and costly. If the book was to be sold, it would provide a financial barrier for people who could not afford to pay its price. It would need to be updated yearly at least, quarterly at best, to provide up-to-date information about new and already approved medications.

5. Telephone Counseling

This distribution option would require that manufacturers, pharmacists, or the Federal Government establish telephone numbers to be staffed by health professionals to answer questions about medications and to send out patient information upon request. Patients could listen to recordings on a number of topics, speak with pharmacists about their prescribed medications, and/or request that written information be mailed or faxed.

The advantage of such a system is that patients could obtain highly specific feedback and interact more fully with a health professional. If a single telephone number was established, patients could call it for ''one-stop health information shopping.'' The system could be self-supporting if patients were charged for the service (e.g., via a 900 telephone exchange). Technicians and health professionals would not have to spend time dispensing individual patient information leaflets.

The disadvantages of such a system are that only those patients who call the number would receive the necessary information. Research has shown that it is difficult for patients to ask questions without having sufficient background about the medication (as would be provided by information provided with dispensed medications). Unless the patient requests a copy of an information leaflet, this alternative does not ensure that patients will receive complete and balanced information (e.g., information about product risks). Charging for the information would be a barrier for those who could not afford the telephone call.

VIII. Proposed Options and Implementation

FDA is proposing regulations that would require manufacturers to provide pharmacists and other authorized dispensers with the means to distribute FDA-approved Medication Guides for their products to help ensure that patients receive adequate information about their prescription drugs. However, FDA is proposing two alternative approaches to how FDA could defer immediate implementation of a comprehensive Medication Guide program for most outpatient drug and biological products. These alternatives are explained in detail in this section.

Regardless of the alternative chosen, FDA is also proposing regulations that would require FDA-approved Medication Guides for products that pose a serious and significant public health concern requiring immediate distribution of FDA-approved patient information. For these products, the regulations would become effective 30 days following publication of the final rule. FDA anticipates that about 10 products or product classes would require such patient labeling each year.

On some occasions, FDA has found it necessary to require that patient labeling be prepared by the manufacturer for distribution with the product because the agency believed that it was in the best interest of the public health for patients to be informed about the product's risks and benefits. In these instances, the agency believes that the risks associated with using the product should be carefully assessed in light of the product's potential benefits for the individual patient. How the information is specifically presented to the patient is particularly important to assure that the patient understands the risks and consequences, including the significance of proper adherence to directions.

FDA intends to use the following criteria to determine what products or classes should be considered for FDA-approved Medication Guides as products that pose a serious and significant public health concern that requires immediate distribution of FDA-approved patient information. FDA seeks comments on the appropriateness of these criteria for selecting products for which FDA-approved patient labeling could be required.

(a) Products for which patient labeling could help prevent serious adverse effects. In these cases, the patient labeling would inform patients about other products or foods which could interact with the labeled product, certain activities (e.g., exposure to the sun, driving) which would increase patient risk, or specific early warning signals indicative of serious adverse effects (e.g., leg pains that could signal a blood clot).

(b) Products that have significant risks about which the patient should be made aware.

(c) Products that pose risks in particular patient populations (e.g., pregnant women, geriatric patients, pediatric patients).

(d) Products for which patient adherence is crucial to either the safety or efficacy of therapy with the product, and for which patient labeling would help increase adherence.

In considering these criteria, FDA may also take into account how many patients use the product. FDA also intends to obtain public input, either through advisory committee deliberations or other public forums, concerning the specific products or classes the agency feels should have FDA-approved Medication Guides. FDA would notify affected manufacturers by letter if and when one of their products is identified as posing a serious and significant public health concern that requires immediate distribution of FDA-approved patient information, and would give the manufacturer sufficient time to produce a draft Medication Guide for agency review.

Application for approval of a Medication Guide would be made via one of two processes, depending on whether the product is already being marketed or is in clinical development, pending approval. FDA believes that in some cases a product already would be on the market when a determination is made that the product poses a serious and significant public health concern requiring immediate distribution of FDA-approved patient information. It is often the case that once a product is used widely in the general population, additional side effects, drug interactions or other effects may be discovered that were not identified during clinical trials of the product. For these products, the manufacturer would submit a labeling supplement to the product's New Drug Application (NDA). In some cases a serious or significant public health concern may arise during drug development, prior to approval. Under these circumstances, the agency may determine that the benefits outweigh the risks, and will approve the product, only if patients are made aware of the potential risks. For these products, the manufacturer would submit a draft Medication Guide as part of the product's NDA.

The agency does not believe that the requirement of a sponsor to prepare a Medication Guide for distribution with the product would pose an undue burden on the sponsor or slow down the approval process. Since patient labeling would be based on the professional labeling, both types of labeling can be developed simultaneously. The Information for Patients section of the professional labeling is already being used by many sponsors to include the kind of information that would be appropriate for inclusion in Medication Guides. However, the agency seeks comments concerning how development of patient labeling could affect approval time or place an undue burden on sponsors.

A. Alternative Approaches

Under Alternative A, implementation of FDA's proposed regulations for a comprehensive Medication Guide program would be deferred if predetermined standards for the distribution of useful patient information are met through voluntary programs within specified timeframes. The agency would periodically evaluate attainment of the performance standards. Proposed performance standards, timeframes and the evaluation process are discussed in detail in this section.

Under Alternative B, FDA would only finalize the Medication Guide program for products that pose a serious and significant public health concern requiring immediate distribution of FDA-approved patient information. The comprehensive program, as it relates to other outpatient products, would not be finalized at this time. Instead, the agency would incorporate the performance standards into a guidance document. The agency would also evaluate, as under Alternative A, whether these performance standards are met in the specified timeframes. If they are not met, FDA would seek public comment on whether the comprehensive Medication Guide program, as proposed in this document, should be finalized and implemented, or whether, and what, other steps should be taken to meet the patient information goals.

B. Performance Standards

The remainder of this section discusses proposed performance standards for assessing the effectiveness of voluntary programs in achieving patient education goals, how performance will be judged against these standards, and how the results of such evaluations will be publicly communicated. It is FDA's intention to work with the private sector to develop reasonable standards that will protect and promote consumer understanding of the directions, uses, and risks of medications, and also to provide periodic feedback so that progress can be monitored and corrective action taken.

As used in this section, the following terms are defined as follows:

''Goal''—the broad objective to be sought. For example, Healthy People 2000 specifies the broad goal that 75 percent of patients should receive useful information.

''Standard or performance standard''—the basic requirement that will be used to judge the degree to which progress has been made toward achieving the specified goals.

''Components''—if there are multiple parts or dimensions upon which performance standards must be judged, the components are an enumeration of each of the parts of a standard. FDA has proposed seven components to the useful information performance standard.

''Criteria''—for each of the components of a performance standard, the basis upon which judgments will be made to determine if the component has been successfully achieved. In this section, FDA lists the seven proposed components of usefulness and describes the criteria that will be used to judge whether each component has been met.

1. Overall Goal

The Public Health Services's (PHS) Healthy People 2000 enumerates a variety of goals which are intended to focus public and private resources on specific and achievable outcomes. Recently, PHS proposed the addition of a new objective, 12.7: ''Increase to at least 75 percent the proportion of people who receive useful information verbally and in writing for new prescriptions from prescribers or dispensers.''

This objective recognizes the need for both oral and written information to be given to patients along with new prescriptions. The distribution rate of 75 percent is clearly delineated. However, the goal does not specify what standards should be applied to determine whether dispensed information is ''useful.''

FDA believes that useful information must be informative and usable by patients to be deemed acceptable for meeting this goal. In section VIII.B.3. of this document, FDA further delineates proposed performance standards that may be used to judge the usefulness of written patient information.

2. Distribution

As the performance standard for distribution of patient information for the year 2000, FDA is proposing to use the Healthy People 2000 goal that at least 75 percent of people receiving new prescriptions are given useful written patient information. In addition, for the year 2006, FDA proposes that the distribution standard be increased such that 95 percent of people who receive new prescriptions also receive useful written patient information.

Generally, FDA envisions that the fulfillment of these standards would entail the distribution of printed information. However, with advancing technology, the development of disease management systems, and the distribution of medication through new distribution channels (e.g., mail-order pharmacies), new technologies may be developed that fulfill the purposes of this standard without requiring paper-based materials. To permit applicability of these standards to a changing patient information landscape, FDA is proposing the following as a definition of receipt of patient information: With new prescriptions, patients must receive permanent, fully portable, and easily accessible media that describe the prescription drug product.

The person who receives the information would be either the patient for whom the product was prescribed or the patient's designee. The information would have to be given to the patient at the dispensing site without the patient's having to actively search for or select the information. The information could be physically handed to the patient or placed in a bag with the prescription in order to meet the distribution standard. However, information that requires patients to select from a display or requires a phone call or return of a postcard would not meet the standard. Permanency of the media means that the information can be repeatedly referenced and can be stored by the patient for future use. Fully portable media means that persons obtaining prescriptions can physically carry the information with them. Easily accessible media means that the information is in a form that can be expected to be readily accessed by patients. Information in the form of a leaflet or brochure would meet the distribution standard, as would an auditory device that plays the message each time a button is pressed. Audiotapes, computer disks, videotapes or other media could potentially meet the standard if the distributor can be assured that the patient has all the devices necessary in his or her residence to use the media distributed.

3. Useful Information

In specifying a performance standard for useful patient information, FDA believes that there are several components that must be taken into account. Each of these components must be satisfactory for FDA to determine that patient information is useful. The seven specific components proposed by FDA include scientific accuracy, consistency with a standard format, nonpromotional tone and content, specificity, comprehensiveness, understandable language, and legibility.

In the section below, FDA further defines each of these components. FDA invites comments on the appropriateness of these standards, components, and criteria proposed to judge overall usefulness of patient information.

FDA further wishes to acknowledge that the specifics of risk information disclosure specified in the performance standards described below may appear to be more detailed than are the specifics of benefits disclosure. FDA believes that it is important to communicate benefits information, as long as it is accurate and is not done in an excessively promotional fashion. FDA believes that the reader will infer many of the benefits of a prescription drug product from the disclosure of how the product is used (its indication). For example, if a product is described as being used to lower high blood pressure, the inference is that use of this medication will benefit the patient by lowering his or her blood pressure, along with reducing whatever additional heart-related risks are associated with uncontrolled elevated blood pressure. FDA also recognizes that benefits inferences that need to be made concerning treatment of certain conditions are more complex and may need to be more specifically defined for the patient. Further, some conditions are more severely debilitating than others. In some cases, it may be appropriate to include relatively more extensive information about the benefits, and to be more reassuring about the risks, of a product, especially when the benefit to risk ratio clearly favors use of the medication.

a. *Scientific accuracy.* (1) Accuracy would be judged by review of the materials for consistency with FDA-approved labeling. Approved uses may be summarized in lay terms (e.g., ''treats certain heart problems'') as opposed to enumerating specific medical indications. However, limitations should also be noted (e.g., ''treats heart disorders'' would not be acceptable). The content of certain patient information may be written to apply to classes of drugs containing products with different indications. In these instances, uses that do not apply to the entire class should be qualified (e.g., ''some,'' or ''certain'' products treat * * *).

(2) Qualifications or limitations regarding the use of the product should be described. For example, if a product is approved for use in conjunction with a dietary or behavioral regimen, the patient information should include reference to such a regimen.

(3) Additional uses that have not been approved by FDA should only be referenced by a general statement (e.g., ''may be used for other purposes as prescribed by your doctor''). Personalized information for individual patients relevant to such a use may be added by a health care provider as a matter of professional practice.

b. *Consistency with suggested format.* The order and headings used should follow those specified for Medication Guides in the final rule (see proposed § 208.22(e)).

c. *Nonpromotional tone and content.* (1) The language used should be educational in nature and avoid ''puffery'' or other promotional terminology. There should be a ''fair balance'' in the description of benefits and risks. The benefits should be described in terms of the uses and effects of the individual medication. Discussion of therapeutic options is acceptable. However, differences among therapies should not be described in terms of express or implied unbalanced comparisons of the advantages of the medication (excepting information supplied for informed consent purposes). For example, phrases such as ''unlike other drugs * * * this drug * * *'' may be perceived as promotional.

Advertising and labeling information directed to patients or consumers, distributed by or on behalf of pharmaceutical manufacturers, must meet the provisions of FDA regulations, including submission for FDA review.

(2) The information should not be misleading in terms of the description of individual drug effects or the overall impression conveyed. Misleading information would include the use of formatting techniques that emphasize benefits and de-emphasize risks.

d. *Specificity.* (1) The information provided should enable a patient to use the product correctly. Proper use includes not only directions for taking the medication, but also information about avoiding negative consequences. Information should also be included regarding proper monitoring of the impact of therapy by correctly interpreting physical reactions to the drug. This would include, for example, informing patients when to call their physician if they do not notice signs of improvement. Risk information should include sufficient detail for an average patient to understand the significance of the hazard described. For example, if a drug causes birth defects when taken in the second or third trimester of pregnancy, users should be expressly informed that the drug may cause birth defects if used after the third month of pregnancy. General references, such as ''tell the doctor if you are pregnant,'' would be insufficient.

(2) Warnings denoting serious or life-threatening effects, even if rare, should be expressly described. This information should not be combined with other information in a fashion that reduces communication of its significance. Additional contextual information should be provided to help patients understand these important risks. This contextual information may include statements of the likelihood of occurrence, the reason why such effects may occur, how to prevent these effects, how to monitor for early warning signs, and/or what to do if such effects occur.

e. *Comprehensiveness.* (1) Information important for the patient to know should be covered in each of the sections of the suggested format. However, it need not be detailed or exhaustive. This would include information necessary for patients to use the drug correctly, to understand important limitations or precautions, and to know the risks that may be assumed by taking the drug.

(2) Long lists of common and infrequent side effects need not be included. The side effects mentioned should include rare, but serious effects as well as common ones. The side effects may be summarized in lay language (e.g., ''blood problems'') and need not be exhaustive. However, the presentation should not diminish communication of the potential hazard. Further, if long lists are included, they should not diminish the significance of major warnings or side effects.

f. *Understandable language.* (1) The information provided should be clearly written for the average person. FDA will not specify a reading level due to concerns about the validity of readability tests as applied to patient drug information. However, the principles of clear writing, as described in a variety of manuals (Refs. 85, 86, 87 and 88) should be followed. Technical terminology should be used only if the terminology is explained and use of the terminology would help the patient understand the material.

(2) Deletion or degradation of important risk, benefit, or directions for use information cannot be justified by the need for language simplification. Additional information, provided through both print and other media, can be used to help communicate to populations with literacy problems.

In general, the information should be likely to be understood by the ordinary individual under customary conditions. While it is clear that many patients will not be able to read English, FDA would not consider this ability as a factor in determining information adequacy. FDA would consider efforts by distributors to communicate with patients of low literacy as consistent with a determination of overall adequacy. Thus, distribution of otherwise

acceptable written materials that utilize simplified language, pictograms, or other communication techniques would be encouraged. Similarly, programs in foreign languages, braille, or other forms of written communication that meet the literacy and information processing needs and ability of selected patient populations would be encouraged.

g. *Legibility.* (1) The information presentation should permit an interested reader to discern the important information. Type size, white space, characters per inch, contrasting colors, and other graphic elements should provide sufficient legibility to enable a typical medication user to read the information. (Note that the typical medication user is often an elderly person with less than perfect vision.)

(2) The layout and graphic presentation should invite readership; interested patients should want to read the material. The graphic presentation should communicate that the material is usable, readable, and comprehensible. The layout should not convey the impression that the material is simply the ''small print'' presented for legal reasons and unnecessary to read. Nor should it convey the impression that the reader would be unable to understand the material because it is too ''dense.''

C. Evaluation

Since the revocation of the PPI regulation in 1982, FDA's evaluation of the extent of distribution of patient information has relied upon national telephone surveys of people who obtained new prescriptions for themselves or a family member at retail pharmacies. This form of research has the advantage of obtaining reports of recent experiences from a representative sample of subjects. The obtained data describe experiences related to obtaining prescription medicines at the pharmacy, licensed practitioner's office, and other self-selected sites. FDA intends to continue using this form of data collection to monitor progress toward meeting the information distribution standard. FDA will also collect and evaluate patient information to determine whether it meets the usefulness standard. FDA will evaluate attainment of these performance standards regardless of whether they are codified in the rule (as under Alternative A) or described in a guidance document (as under Alternative B).

1. Measurement of Distribution Rates

FDA anticipates conducting three iterations of these national surveys in the approximately 11 years following publication of the final rule. The first iteration will be conducted along with a concomitant ''pharmacy shopping'' survey, to validate distribution elements obtained by the national telephone survey. The second iteration will be conducted in approximately the year 2000. The distribution rates obtained from this iteration will be used to help determine whether the standard of useful information distribution that would result in continued deferral of further FDA action toward implementing (Alternative A) or finalizing and implementing (Alternative B) a comprehensive mandatory program has been met. Similarly, the third survey iteration will be conducted approximately 6 years later. Together with the results of FDA's evaluation of patient information usefulness, the distribution rates obtained from this final iteration will determine whether the standard of useful information distribution has been attained.

FDA encourages interested groups to sponsor similar distribution rate evaluations in the intervening years to achieve a more complete picture of the effectiveness of information distribution of the voluntary programs. FDA will make its methodology and survey questionnaire available to the public and will provide technical assistance to any party interested in using this procedure.

One major limitation of the survey is that patient reports obtained over the telephone cannot detail the type of information disseminated. Further, these reports rely on patient memory, which may be subject to distortions. Therefore, FDA will conduct a one-time-only pharmacy ''shopping'' survey to validate the telephone interviewing data related to the distribution of written information with dispensed new prescriptions. This will be a multiple city survey. Observers will pose as patients and fill prescriptions for a commonly used drug. The observers will collect written information disseminated to patrons. They will also record oral interactions with pharmacy personnel and the existence of collateral information available to patients.

Although FDA would also prefer to validate the reported data concerning oral and written information obtained at the licensed practitioner's office, there are numerous cost, methodological, and logistical barriers to a data collection of such size and complexity. FDA invites comments about the advisability of, and recommendations for how to accomplish, validating these data.

Data from the shopping survey will be analyzed in conjunction with a concomitant telephone survey to validate self-reported rates and to help understand the degree to which any reporting biases may influence the telephone survey results. The shopping survey will also obtain information about the use of various commercial information systems at pharmacies across the country. These data, along with obtainable industry-trend data, will be used to project national totals of the degree to which information is being disseminated to patients.

FDA will also collect sample patient information pieces from commercial suppliers. The initial data collection will occur immediately following publication of the final rule, with additional collections occurring at 2-year intervals. Sample information sheets will be obtained for commonly used medications. Rarely used medications (not in the top 500 most commonly prescribed) and medications for which patient information may be problematic (e.g., cancer chemotherapy, major psychotropic medications) will not be included in these samples.

FDA will estimate the extent to which each system is used nationally. FDA will also estimate the percentage of prescriptions delivered through other distribution channels (e.g., mail-order pharmacies, dispensing physicians) and the extent to which different patient information systems are used in these distribution channels.

2. Determination of Information Usefulness

FDA will determine the degree to which obtained samples of patient information meet the performance standard of useful information. The samples will be evaluated on each component, using the criteria described above. Each sample will be scored on each criterion, using ''acceptable'' and ''not acceptable'' cutoff points. As mentioned, FDA believes that for a particular information sheet to be judged as acceptable overall, it must receive an acceptable rating on each of the individual components. However, the agency solicits comments regarding this rule of operation.

In addition, FDA solicits comments regarding how many and what type of drug products should be included in the patient information review, and how each component of usefulness should be scored. FDA also intends to hold a Part 15 Hearing or other public forum where interested parties could provide recommendations and rationale for usefulness components, associated criteria, and ratings systems for patient information.

D. Feedback and Application of Standards

1. Reporting the Evaluation Results

Approximately every 2 years, FDA will issue a report on the overall acceptability of written information, including ratings on each of the components of usefulness. Newly updated distribution rates will also be reported in relevant years (i.e., with the first, third, and sixth information evaluations). In these years, the report will also provide oral counseling rates.

FDA intends to estimate the percentage of patients receiving useful information by multiplying the percentage of patients stating that they received written information in the national survey by the percentage of patient information sheets judged as useful (weighted by estimated distribution rates for the sheets and the overall usefulness rating for the sheets).

FDA plans to issue a report discussing the results of each survey. The report will be in sufficient detail to permit an analysis of the basis of the computed percentages. It will also describe the analysis of each information sheet's performance on each of the usefulness components.

2. Report Implications

If Alternative A is selected, FDA will continue to defer the implementation date for the full Medication Guide program (except for the section that requires Medication Guides for specific drugs which FDA has determined have serious and significant public health concerns requiring immediate distribution of FDA-approved patient information) if the third evaluation report indicates that 75 percent of patients receive useful information. FDA will continue to conduct these surveys every 2 years. If the sixth evaluation report indicates that 95 percent of patients receive useful information, FDA will propose revocation of the sections of the rule that provide for implementation of a comprehensive Medication Guide program.

If Alternative B is selected and the third evaluation report indicates that 75 percent of patients receive useful information, FDA would continue to leave unfinalized the proposal for a comprehensive Medication Guide program. If this goal is not met, FDA would seek public comment on whether the comprehensive Medication Guide program, as proposed in this document, should be finalized and implemented, or whether, and what, other steps should be taken to help ensure that the goal is met. A similar judgment will be made based on whether the sixth evaluation report indicates that 95 percent of patients receive useful information.

In extrapolating from sample statistics to population parameters, all measurement involves a certain degree of imprecision. An estimate of expected sampling error for a simple random sample of 1,000 would be approximately plus or minus 3 percentage points of the sample statistic. FDA is proposing to use a relatively inclusive plus or minus 5 percentage points as the acceptable error (confidence interval at $\propto$=.95) for the standards for information distribution. Using this interval means that the year 2000 standard would be met if it was determined that between 70 percent and 80 percent of patients received useful information. The year 2006 standard would be met if it was determined that between 90 percent and 100 percent of patients received useful information. FDA requests comments concerning whether this is the most appropriate confidence interval to use.

Given the time necessary to implement an adequate patient information program, by either a mandatory program or a continuation of voluntary programs, FDA anticipates that the great majority of patients should receive useful patient information by approximately 10 years after the effective date of a final rule based on this proposal.

E. Medication Guide Program

The regulations set forth in this proposal describe a program that requires manufacturers to prepare FDA-approved patient labeling (Medication Guides) for their prescription drug products. The regulations specify the format and content for such information. They further specify that manufacturers must provide drug distributors and authorized dispensers with sufficient copies of these Medication Guides, or the means to produce sufficient copies, such that each patient receives a Medication Guide with dispensed new prescriptions and upon request with a refill.

Under Alternative A, in the event that the distribution and/or ''useful'' performance standards previously described are not met, the final regulation based on this proposal (mandatory program) would be fully implemented. An announcement of the institution of such a program would be issued concurrently with the third or the sixth evaluation report notice published in the **Federal Register** (no sooner than 5 years or, if the rule continues to be deferred after the third evaluation report, 11 years after the effective date of the final rule).

To implement this requirement, New Drug Application (NDA) applicants and holders would be required to submit draft Medication Guides for all submissions for new molecular entities (NME's) and for new indications for approved products. In addition, concurrent with an announcement that the regulations will be fully implemented, FDA would publish an implementation schedule. This schedule would require that application holders submit draft Medication Guides for specified NDA's. FDA envisions that such a schedule would be based upon the most frequently used products at the time. In order to avoid problems with uneven competitive requirements, FDA would also consider the simultaneous review of products within the same pharmacological or therapeutic category.

Once an innovator drug Medication Guide was approved, manufacturers of generic versions of the drug would also be required to prepare and distribute Medication Guides modeled after the innovator's approved Medication Guide.

Given the large number of drugs on the market, FDA envisions that it would take approximately 10 years to complete approval for the vast majority of Medication Guides. However, by implementing the Medication Guide requirement as a function of the most popularly used products first, a larger percentage of dispensed prescriptions would be covered.

Under Alternative B, if the distribution and/or ''useful'' performance standards are not met, FDA would seek comment on whether the proposal requiring a comprehensive Medication Guide program, as described in this document, should be finalized and implemented, or whether, and what, other steps should be taken by FDA to ensure that the patient information goals are met. Subsequent to this comment period, either the Medication Guide regulations proposed in this document would be finalized and implemented, or FDA would repropose a different approach to helping to ensure attainment of the specified goals.

IX. Conclusion

The long history of PPI's demonstrates that disagreements between the public and private sectors in determining the best approach for providing patient information have not served patients well. Since the issue was first discussed in the 1970's, virtually all interested parties have agreed that there is a critical need to better inform patients

about their medications. Most of those who opposed PPI's accepted the premise that patients needed to be better informed. However, opponents argued that the private sector could do a better job of educating patients if left unencumbered by Federal regulations. FDA came to the same conclusion and withdrew requirements for the program. In the ensuing decade, however, evaluations demonstrate that although many private sector programs have been initiated, their impact on patient education has been disappointingly low.

In the last 2 years, however, the increasing computerization of pharmacies together with OBRA '90 requirements have apparently contributed to an increase in the provision of oral and written patient information. However, FDA's review of popular commercial systems in use indicates that the quality of information provided is uneven. In the interests of encouraging a continuation of this distribution trend, and improving the value of the information to patients, FDA has concluded that both standard-setting activities and the addition of a strong incentive are appropriate and necessary.

Prior to developing this proposed rule, FDA met individually with representatives of the pharmacy, pharmaceutical industry, patient information producer, medical, and consumer communities. All of the represented constituencies at these meetings indicated that they wanted health professionals to provide patients with useful written prescription drug information.

As mentioned above, in addition to soliciting written comments, FDA intends to hold a Part 15 Hearing to solicit a broad range of views about how best to measure usefulness of individual patient information pieces. It should be clear to all parties, however, that FDA's concern is not with the distribution of pieces of paper, but with the education and empowerment of patients. Therefore, FDA intends to expand this dialogue to solicit new ideas and feedback about other aspects of this proposal, such as how medication adherence can be more effectively facilitated, and new ideas about how to communicate information to patients. FDA believes that presentations based upon research with patients and consumers will be especially important; thus, FDA will actively solicit such information. Developing systems that make maximal use of technology and can be flexibly adapted to all patients, thus providing useful and specific information, is the goal of FDA's broader commitment to improving patient information. This goal will take an active partnership to meet; it cannot be achieved by FDA alone.

Private sector efforts also will be needed to improve the basic mechanism through which patient education about prescription medicines occurs, i.e., oral counseling. In addition, programs are needed to stimulate discussions about medications by health care professionals when the medications are initially prescribed. Organizations that can help determine the best mechanism for health professionals to introduce and discuss patient medication information with patients would be vital to the success of the program.

Additional programs also will be needed to provide educational aids to patients with literacy problems to help them utilize medication information most effectively. These programs must be diverse and targeted to address the particular deficiencies causing the literacy problem.

Data from the recent survey ''Adult Literacy in the United States'' (Ref. 72) indicate that most of the individuals who perform at the lowest level of proficiency (from 66 to 75 percent) described themselves as able to read or write English ''well'' or ''very well.'' They did not view themselves as deficient in any substantive fashion. It would be inappropriate for health care professionals to withhold information from patients merely on the premise that they may have some difficulty understanding the information. Even with basic skills, interested patients would be able to profit to some extent from the documents. With additional help, the vast majority of patients would be able to profit from improved information.

Of major importance to the success of improved patient information would be private suppliers or organizations that can help pharmacies, physicians' offices, and managed care organizations store, access, produce, and/or distribute medication information. Groups that can provide customized services to meet the individual needs of the vast array of authorized dispensers would be of great service to help this community meet the desired objectives. Such groups could expand the provision of other information, such as disease information or general information about using medicines safely, which would augment the educational benefit for patients.

FDA welcomes comments about these topics and remains dedicated to forging a medicine information delivery system that encourages, and does not retard, the development of innovative communication systems.

X. Description of the Proposed Rule

The proposed rule, if finalized, would require a Medication Guide for certain human prescription drug products, including biological products. The rule would require manufacturers to prepare and distribute, or provide the means for distributing, a Medication Guide that would accompany prescription drug products that patients receive and use on an outpatient basis without the direct supervision of a health care professional. Medication Guides would be distributed with all new prescriptions and with refills when requested by the patient.

Under Alternative A, the provisions in the proposed rule would be deferred for a majority of the prescription drug and biological products that otherwise would be affected in order to give voluntary efforts an opportunity to achieve specific goals of distribution of useful drug information within specified timeframes. The agency will measure the success of the voluntary efforts by establishing performance standards that measure both the distribution of patient medication information and information usefulness. The agency will conduct periodic evaluations to measure whether the performance standards are met and will issue reports of the findings. If the performance standards are not met by the end of each of two specified timeframes, the provisions of the rule would be implemented.

For products that pose a serious and significant public health concern requiring immediate distribution of patient information the provisions would be implemented 30 days following publication of the final rule.

Under Alternative B, FDA would also give voluntary efforts an opportunity to achieve the goals of distribution of useful information within specified timeframes. The difference, however, is that under this option the agency does not intend to finalize immediately the proposed performance standards, or the sections that defer implementation, in the form of a regulation. Instead, the agency intends to use the proposed performance standards as guidance for the private sector. If the performance standards are not met at the specified times, then the agency will seek public comment on whether a comprehensive Medication Guide program, as described in this proposal, should be finalized and implemented or whether, and what, other steps should be taken to meet the patient information goals.

For Alternative B, FDA, however, does intend to finalize the requirement for products that pose a serious and

significant public health concern requiring immediate distribution of FDA-approved patient information. This provision would be implemented 30 days following publication of the final rule.

To be of value, product information must be understandable to patients. The use of overly technical language may deter patients from reading important information. Therefore, the proposed rule would require that the Medication Guide be written in nontechnical language, be nonpromotional in tone or content, be based on the professional labeling for the drug product, and be presented in a uniform format.

The Medication Guide would contain a summary of the most important information about a drug product, including the approved uses for the product, circumstances under which the drug product should not be used, serious adverse reactions, proper use of the product, cautions related to proper use, and other general information.

Parties would be permitted to request an exemption for a particular drug product from any of the specific requirements of the proposed rule. The proposed rule would also permit the agency to exempt or defer certain drug products from the requirement of a Medication Guide.

The proposed rule would require manufacturers to provide directly, or supply the means to provide, sufficient numbers of the Medication Guide to the distributor or dispenser of a prescription drug product. The dispenser, in turn, would be required to provide the Medication Guide to the patient. FDA is proposing to exempt qualifying small retail pharmacy outlets from the requirement to dispense a Medication Guide, except for products packaged in unit-of-use containers and for products which the agency determines must be dispensed with a Medication Guide.

Specific provisions of the proposed rule are as follows:

A. Scope and Implementation

Proposed § 208.1(a) would limit the Medication Guide requirements to human prescription drug products, including biological drug products, administered primarily on an outpatient basis without the direct supervision of a health professional. FDA is proposing this limitation because, as discussed earlier in this preamble, the agency believes that patients generally seek and are ready to receive and understand information about their drug products after they have received them. The Medication Guide would serve as an at-home reference for patients when they are ready to self-administer products. The proposed rule requires that a Medication Guide be dispensed with new prescriptions, and with refills if requested by the patient. The proposed rule would not apply to prescription drug products administered in licensed practitioners' offices or institutional settings, such as hospitals, nursing homes, or other long-term care facilities, because FDA believes that the continuous presence of health professionals in these settings gives patients the opportunity to ask questions about their prescription drug products. The proposed rule also would not apply in emergency situations because FDA believes distribution of the Medication Guide in such situations would be impractical. FDA has also provided an exemption for small retail pharmacy outlets. Other dispensers which meet the small business criteria set forth in the regulations would also qualify for such an exemption.

Proposed § 208.1(b) defers the implementation of the Medication Guide provisions for all affected drug and biologic products, except for the § 208.1(d) products, until a determination is made by FDA that certain performance standards have not been met.

Proposed § 208.1(b)(1) would provide for the Medication Guide provisions for all but the § 208.1(d) products to be deferred if 75 percent of the patients receiving new prescription drugs or biologics covered under these provisions receive useful patient information 5 years from the effective date of the final rule. If this standard is met, FDA would continue to monitor the voluntary efforts for distributing patient information. As proposed in § 208.1(b)(2), if, after an additional 6 years, 95 percent of the patients receiving new prescription drugs or biologics covered under these provisions receive useful patient information, the Medication Guide provisions would continue to be deferred, except for the § 208.1(d) products.

As described in greater detail previously, the agency will evaluate both the distribution and usefulness of the information with regard to specific criteria. Proposed § 208.1(c) includes the seven proposed components of the usefulness standard. An extensive discussion of the specific criteria the agency proposes to use in evaluating achievement of the usefulness standard is found in section VIII. of this document. FDA is considering whether the details of these criteria should be restated in the codified language, and invites comment on this issue.

Under Alternative A, if both of the requirements in proposed § 208.1(b) are met, the provisions of this part would be deferred for all products except those that the agency determines pose a serious and significant public health concern requiring immediate distribution of patient information. In addition, under Alternative A, if both of the requirements in proposed § 208.1(b) are met, the agency intends, at that time, to initiate notice and comment rulemaking to revoke § 208.1(b)(1) and (b)(2).

As discussed previously, under Alternative B, the agency does not intend to finalize § 208.1(b) and (c) immediately. Rather, if the performance standards set forth in proposed § 208.1(b) and (c) are not met, the agency will again seek public comment on whether a comprehensive mandatory Medication Guide program, as described in this document, should be implemented or whether, and what, other steps should be taken to meet the goals.

Under both alternatives, proposed § 208.1(d) would allow FDA to require that FDA-approved Medication Guides be distributed with certain prescription drug products. See Section VIII. of this document for a discussion of the criteria that would be used to determine the types of products that may fall under § 208.1(d).

B. Definitions

Proposed § 208.3(a) would define ''authorized dispenser'' as an individual who may legally dispense prescription drug products. FDA believes that, in most instances, the authorized dispenser will be a pharmacist.

Proposed § 208.3(b) would define the phrase ''dispense to patients'' as the act of delivering a prescription drug product to a patient or an agent of the patient. Because the proposed rule would apply only to drug products dispensed on an outpatient basis without the direct supervision of health care professionals, proposed § 208.3(b) limits the scope of ''dispensing.'' For instance, the definition of the phrase ''dispense to patients'' does not include the delivery of a nonprescription drug product.

Proposed § 208.3(c) would define ''distribute'' as ''the act of delivering (other than by dispensing) a drug product to any person.''

Proposed § 208.3(d) would define ''distributor'' as a person who distributes a drug product. FDA notes that its interpretation of a distributor has traditionally included repackers, and would do so here.

Proposed § 208.3(e) would define ''licensed practitioner'' as an ''individual licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to prescribe drug products in the course of professional practice.''

Proposed § 208.3(f) would define ''manufacturer'' as described in §§ 201.1 and 600.3(t) of this chapter.

Proposed § 208.3(g) would define ''patient'' as any individual with respect to whom a drug product is intended to be, or has been, used.

C. Content of a Medication Guide

Proposed § 208.20 would describe the content of a Medication Guide. As stated earlier, FDA believes that the information in a Medication Guide must be written in language that is easily understood by patients. To ensure that information in a Medication Guide provides a comprehensible and objective description of the drug product, proposed § 208.20(a)(1) would require that information be written in English, presented in lay language, and would prohibit the use of promotional language.

While FDA acknowledges that there is a significant minority of U.S. citizens who speak Spanish as their primary language, it hesitates to impose the additional burdens on manufacturers and dispensers that would result from requiring the availability of Medication Guides written in Spanish for these individuals. FDA also recognizes the many other population segments who do not speak English as their primary language. FDA requests comments concerning how it can most fairly and effectively communicate patient medication information to these populations.

Under proposed § 208.20(a)(2), the Medication Guide must be based on, and must not conflict with, the approved professional labeling for the drug product. The Medication Guide should, in general, provide a lay ''translation'' of those portions of the professional labeling that are important for effective consumer understanding and use of the product. This ''translation'' may include sufficient background information or context to facilitate consumer understanding. Proposed § 208.20(b) lists specific types of information that must be included in a Medication Guide. Under proposed § 208.20(b)(1), the Medication Guide would be required to identify the drug product brand name (e.g., trademark name or proprietary name), if any, and established name. If the product does not have an established name, the proposed rule would require that the drug product be designated by its active ingredients. In addition, the Medication Guide would include the phonetic spelling of the brand name or the established name, whichever name appears throughout the Medication Guide.

Because many people take a number of drug products, FDA believes that it is important that patients be easily able to match a drug product with the correct Medication Guide. Information could include the color, shape, markings, and, if applicable, the drug product's code imprint. There are a number of possible ways to provide this information including: (1) A separate identification section, (2) including the information in the personalized section (this optional section of the Medication Guide is explained later in the preamble to this proposal), or (3) providing preprinted stickers that would be placed on the appropriate Medication Guide by the dispenser. An example of one way to provide product identification information is displayed in the sample Medication Guides in Appendix C.

Proposed § 208.20(b)(2) would require a brief section concerning the most important aspects of taking the drug product. This would include the product's approved indications, especially important instructions for proper use of the drug, and any significant warnings, precautions, contraindications, serious adverse reactions, and potential safety hazards.

Proposed § 208.20(b)(3) would require the Medication Guide to contain a statement identifying the product's indications, that is, the uses identified in the indications and usage section of the approved professional labeling. The Medication Guide may summarize indications or omit rarely prescribed indications.

Proposed § 208.20(b)(4) would require the Medication Guide to identify the conditions under which the drug product is not to be used for its labeled indications, i.e., contraindications to the product's use. In nontechnical language, the labeling would describe the contraindications specified in the professional labeling for the drug product, reminding the patient, for example, to provide the licensed practitioner with relevant medical history or information about other drugs the patient is taking that may pose a significant contraindication. Contraindications to use may include a previous allergic reaction to the product, pregnancy, the patient's use of certain other medications, or a particular condition that might make the drug product less effective or dangerous.

Proposed § 208.20(b)(4) would also require inclusion of the steps the patient should take to remedy the situation should any of the listed circumstances apply. This may include consulting with his or her licensed practitioner before taking the drug, discontinuing use of the product, etc.

Proposed § 208.20(b)(5) would require the Medication Guide to describe precautions related to the proper use of the drug product. Under proposed § 208.20(b)(5)(i), these precautions would include activities the patient should avoid while taking the drug product, such as driving or sunbathing, and list other drugs, foods, or substances, including alcohol or tobacco products, the patient should avoid because they may interact with the drug product. The information would help patients use the drug product in a way that would promote its safety and effectiveness.

Under proposed § 208.20(b)(5)(ii), the Medication Guide must also contain a statement regarding the product's use in pregnant women. The statement must discuss any risks to the pregnant woman or the fetus. Proposed § 208.20(b)(5)(iii) through (b)(5)(vi) would also require the Medication Guide to contain, if appropriate, precautionary information about risks to a nursing infant, and any information on use and risks for pediatric, geriatric, or other identifiable patient populations.

Proposed § 208.20(b)(6)(i) would require the Medication Guide to list and describe adverse reactions associated with the use of the drug product that are serious or occur frequently. This information would be presented in a manner that would help patients understand and remember it. Material presented under this provision would restate, in nontechnical language, the information regarding the most significant warnings and adverse reactions specified in the professional labeling. In addition, where appropriate, the Medication Guide should inform the patient what to do if they occur.

Organizing and explaining adverse reaction information for different drug products may vary. For example, adverse reactions might be organized by the organ systems in which they occur, by their severity, by the frequency with which they occur, by a combination of these approaches, or by any other appropriate method that would provide patients with the information. In contrast to the professional labeling, which often contains an exhaustive list of associated adverse reactions, regardless of their frequency, the Medication Guide should only list those adverse reactions that are meaningful to

the patient, in terms of seriousness, and/or frequency.

Proposed § 208.20(b)(6)(ii) would require the Medication Guide to discuss the risks, if any, to the patient of developing a tolerance to or a dependence upon the drug product.

Proposed § 208.20(b)(7) would require information concerning the proper use of the drug product. Studies indicate that many patients do not take prescription drugs properly (Refs. 3 and 4). Consequently, proposed § 208.20(b)(7)(i) would require a statement stressing the importance of adhering to the dosing instructions. Under proposed § 208.20(b)(7)(ii), the Medication Guide would also contain any special instructions on how to administer the drug; for example, proper dosing intervals, whether the drug should be taken with food, or at a period of time before or after eating. For products such as inhalers, injectables, skin patches, and so on, that have special instructions for administration, these instructions should be referenced in the Medication Guide.

Proposed § 208.20(b)(7)(iii) would require a statement of what a patient should do in case of an overdose, i.e., contact the local poison control center or hospital emergency room. Since FDA notes that a significant number of patients fail to adhere to the dosing regimen, proposed § 208.20(b)(7)(iv) would require a statement of what a patient should do if the patient misses taking a scheduled dose.

Proposed § 208.20(b)(8) would also require the Medication Guide to contain general information about the safe and effective use of prescription drug products.

Patients may become concerned if their Medication Guide does not include the purpose for which their health professional prescribed the product. Therefore, proposed § 208.20(b)(8)(i) would require inclusion of the verbatim statement that ''Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.'' This statement would be juxtaposed with a statement encouraging the patient to discuss any questions or concerns about the drug product with a health professional.

Although health professionals understand that approved products may be prescribed for other than FDA-approved indications, patients typically do not possess this knowledge. Therefore, it is appropriate to advise them of this fact, and that they should bring any concerns they may have to the attention of a health professional. FDA believes that these disclosures provide the necessary context to ensure that patients will comprehend effectively medication information. The agency stresses, however, that such ''contextual'' disclosure is inappropriate for professional labeling, which is directed at health professionals who are already aware of their freedom to prescribe medicines as they see fit, as part of the practice of their profession.

FDA also notes that this statement is an acknowledgment about the use of medicines in general, not about any particular product. The agency will not sanction the use of this or similar statements concerning unapproved uses in promotional labeling and advertising for specific products.

Proposed § 208.20(b)(8)(i) would also require a statement noting that professional labeling for drug products may be available from the patient's authorized dispenser or licensed practitioner. Many individuals, including some pharmacists and licensed practitioners, erroneously believe that State or Federal law prohibits providing a drug product's professional package insert to patients. Moreover, the professional labeling for a drug product provides the most detailed and comprehensive information about prescription drug products and should be available to any patient upon request. Although the professional labeling for a drug product may be too technical for many patients to understand, patients should be encouraged to learn more about their medications and may seek to examine professional labeling. Authorized dispensers and licensed practitioners are able to answer questions about the professional labeling and thereby reduce the amount of confusion produced by its technical language.

Proposed § 208.20(b)(8)(ii) would require a statement informing the patient that the drug product has been prescribed for the sole purpose of treating the patient's condition and must not be used for other conditions or given to other persons. This statement is intended to caution against the dangers of self-diagnosis and lay diagnoses in general. A licensed practitioner prescribes a particular drug to treat a certain condition in a certain individual. Use of the drug by lay persons to treat another condition in the same individual may be, at best, ineffective and, at worst, directly hazardous to a patient's health or indirectly hazardous by delaying proper diagnosis and treatment. Use of the drug by another individual, without a professional evaluation of the individual's medical condition and history, could be life-threatening.

Section 208.20(b)(8)(iii) would require the manufacturer's, packer's, or distributor's name and address; or the name and address of the dispenser of the drug product; or for biological products, the name, address, and license number of the manufacturer. This information could assist the manufacturer or distributor and FDA in tracing and, if necessary, recalling the drug product. Furthermore, providing names and addresses would enable patients to contact a manufacturer or distributor if they have any questions about the drug product.

Section 208.20(b)(8)(iv) would require the date of the most recent revision to the Medication Guide. This will enable patients and authorized dispensers with multiple versions of a Medication Guide to determine which Medication Guide contains the most current information.

The contents of a Medication Guide may vary based on the product's dosage form, bioavailability, or extent of systemic exposure, as stated in the product's labeling. For example, some topical prescription drug products that are not systemically absorbed may not require a statement regarding the activities, drugs, foods, or other substances that a patient should avoid when taking the drug product, or information on risks from use of the drug product during pregnancy, labor, delivery, or nursing. FDA encourages manufacturers, distributors, and others who have questions on the preparation or content of their Medication Guide to contact FDA.

The Medication Guide shall be dispensed as approved by FDA without the inclusion of any additional information. However, authorized dispensers may, and are encouraged to, personalize the Medication Guide document by including, for example, the prescription number, the name, address, and/or telephone number of the authorized dispenser and/or licensed practitioner, and information personally identifying the patient and relevant demographic or medical information (that does not violate the patient's privacy). This information may precede or follow the required information in the Medication Guide, but in no instance should the information be more prominent or obscure any required information. Authorized dispensers and licensed practitioners are also permitted and encouraged to supply special instructions regarding the product's use directly before or following information in the Medication Guide.

D. Format for a Medication Guide

FDA believes that the Medication Guide should have a uniform format so

patients can become familiar with the type and location of specific information. The proposed rule would require the Medication Guide to contain identical section headings, a consistent order of information, the use of highlighting techniques, and a minimum type size.

A ''shell'' of the proposed uniform format is displayed in Appendix A of this document. FDA chose different drugs to illustrate the uniform format, and these examples may be found in Appendix B of this document. Examples of the Medication Guide using alternative formats are displayed in Appendix C of this document. FDA invites comment on these alternative formats. These Medication Guide models were prepared solely by FDA for illustrative purposes and do not represent approved labeling by the agency.

The proposed rule would allow the Medication Guide to reach consumers through a variety of methods, ranging from traditional preprinted inserts to state-of-the-art, computer-generated material. The agency recognizes that the level of information technology varies widely across the country. For instance, while most pharmacies are now equipped with computers, both the ability to access outside materials and the print quality of computer-generated documents can vary greatly. Thus, the proposed Medication Guide regulations are designed to accommodate these varying levels of technology and not hinder technological advances or improvements in the transmission of patient information.

Proposed § 208.22(a), would establish a minimum 10-point type size for the Medication Guide (1 point = 0.0138 inches). This requirement applies to all sections of the Medication Guide except the name and address of the manufacturer and the revision date. FDA believes that this type size is necessary to facilitate easy reading by elderly patients. However, as legibility is determined by additional graphic factors, proposed § 208.22(b) would require that the print be legible and clearly presented.

Additionally, FDA is proposing to amend the professional labeling regulation at 21 CFR 201.57, which requires the professional labeling to reprint, in its entirety, any patient labeling for a drug product. The proposed amendment would clarify that the 10-point minimum type size does not apply to any patient labeling or Medication Guide that is reprinted in the professional labeling.

FDA recognizes that the communication of important information requires graphic emphasis to highlight certain portions of the text. The graphic emphasis selected should be appropriate to the particular method of printing the Medication Guide. Thus, while multiple colors may be used for emphasis in preprinting the Medication Guide, the use of dot-matrix computers would require boldfacing, underlining, or some other highlighting method.

As stated earlier in the preamble, the agency acknowledges that there are many forms of commercially available, consumer-oriented medication information. To enable patients to recognize that the Medication Guide is the ''official'' patient labeling for a particular drug product, proposed § 208.22(c) would require every Medication Guide to contain the words ''Medication Guide'' prominently at the top of the first page of each Medication Guide. It would also require, at the bottom of the Medication Guide, the verbatim statement that ''This Medication Guide has been approved by the U.S. Food and Drug Administration.'' Section 208.22(d) would require the brand and established name to be prominently displayed. The established name shall not be less than one-half the height of the brand name.

In order to organize the information in the Medication Guide, proposed § 208.22(e) would require that the content requirements listed in § 208.20 be placed under specified headings. These headings would also be placed in a specified order so that the patient can easily find the information. The proposed headings are in question form and would include:

(1) ''What is the most important information I should know about (name of drug)?;''

(2) ''What is (name of drug)?;''

(3) ''Who should not take (name of drug)?;''

(4) ''How should I take (name of drug)?;''

(5) ''What should I avoid while taking (name of drug)?;''

(6) ''What are the possible side effects of (name of drug)?''

The Medication Guides for certain drugs may require additional headings, e.g., ''How should I store (name of drug)?'' (See Ceclor for oral suspension draft Medication Guide in Appendix B of this document.)

The agency invites comments on alternative headings. Examples of alternative headings appear in the Medication Guide models published in Appendix C of this document.

In developing these model Medication Guide formats, FDA has reviewed the formats used in a variety of patient information leaflet systems and in patient information books. The agency has tentatively concluded that the preferred format is the one that provides consumers with questions about their medication and answers to these questions and that organizes the information in a way similar to the professional labeling. This will help manufacturers to prepare the Medication Guide and place information in a consistent section of the Medication Guide. Patients will obtain information that is consistent with professional labeling. FDA intends to evaluate this (and other possible) formats during the comment period for this proposal.

FDA recognizes that there are important differences between labeling directed toward professionals and the Medication Guide directed toward patients. The format for the Medication Guide should help emphasize the most important information the patient needs to know to use the drug product properly and to communicate with his or her health care professional. Major sections of the professional labeling, such as the Clinical Pharmacology section, that are useful to health care professionals, are not likely to be as useful to patients (although conclusions from that section, such as effects of food on absorption, may be important). Similarly, other information, such as complete lists of reported adverse reactions, may overwhelm the patient or obscure the most important information. Thus, to facilitate the communication of information to patients in a meaningful fashion, the Medication Guide will be expected to summarize and distill the contents of the professional labeling into terms that are more understandable and useful to the layperson. On the other hand, it is not expected that the Medication Guide will omit serious or potentially adverse consequences of using the medicine that are important for patients to know.

FDA will also permit the addition of ''contextual'' information, not included in the professional labeling, to help patients understand the labeling information despite their lack of background and training in medicine.

FDA is aware that excessive length may discourage use of Medication Guides and interfere with the communication of important messages. FDA will therefore attempt to limit the amount of information included in the Medication Guide, focusing on and emphasizing the most important information for the patient (e.g., by changes in typeface, use of white space or contrast, underlining). The Medication Guide samples reprinted in the appendices to this document

provide examples of how FDA believes a Medication Guide should be formatted, composed, and otherwise structured for the patient. In addition to inviting general comments on these formats, FDA invites comments on whether the Medication Guide should be printed on paper of a specific size and whether a page limit (e.g., two pages) is appropriate.

E. Distributing and Dispensing of a Medication Guide

The proposed rule is intended to ensure that consumers receive patient labeling information, but permits manufacturers, distributors, and dispensers to provide information in addition to that required under the proposed rule. The agency has designed the distribution and dispensing requirements to be flexible and to accommodate the increased use of computers and other technological advances in pharmacies.

Proposed § 208.24(a) would establish distribution requirements for drug products in finished dosage form that are packaged in large volume containers. Under the proposal, a manufacturer that ships a large volume container of a finished dosage form to a distributor or an authorized dispenser would be required to provide the Medication Guide in sufficient numbers, or the means to produce the Medication Guide in sufficient numbers to enable the authorized dispenser to provide a Medication Guide to each patient receiving the drug product.

The reference to the ''means to produce the Medication Guide in sufficient numbers'' signifies that a manufacturer is not limited to providing hard copies of the Medication Guide to its distributors and authorized dispensers. Instead, the manufacturer can satisfy its distribution requirements by giving distributors and authorized dispensers the ''means'' to produce the Medication Guide in sufficient numbers. For example, the manufacturer could provide computer software that enables the distributor or authorized dispenser to print the Medication Guide. However, FDA cautions that if a manufacturer elects to give distributors and authorized dispensers the ''means'' to produce the Medication Guide, it must give the individual distributor or authorized dispenser an effective means, including resources and materials, to produce the Medication Guide. In other words, FDA would not consider a manufacturer to have complied with its regulatory obligations if it gave incompatible software to a distributor or authorized dispenser or provided items that would require the distributor or authorized dispenser to purchase other machines, goods, or services in order to produce a Medication Guide.

For each drug product requiring a Medication Guide, proposed § 208.24(a)(2) would require manufacturers to place a label on each large volume container of finished dosage form instructing authorized dispensers to distribute the Medication Guide. This is necessary because FDA intends to phase in Medication Guide requirements, and authorized dispensers will need to know which drug products have required patient labeling and which ones do not yet have such requirements.

The proposed rule would establish similar requirements for distributors who provide drug products to authorized dispensers.

FDA recognizes the complexity of the drug distribution system and encourages the development of innovative methods to meet the requirements of this section. The agency intends to consult with interested parties so that distribution problems may be identified and solutions developed.

For drugs in unit-of-use containers, proposed § 208.24(c) would require the manufacturer and distributor to provide the Medication Guide with each package that is intended to be dispensed to patients. The agency notes that this requirement, if finalized, would be consistent with EC requirements on patient leaflets in unit-of-use packaging.

The proposed rule, at § 208.24(d), would also enable manufacturers and distributors to have other persons meet their distribution and dispensing requirements. For example, manufacturers could enter into a contract with a third party to provide the Medication Guide to distributors and dispensers. Such third party information systems already exist in other contexts; for example, the agency is aware that a third party vendor routinely collects and publishes drug identification information which poison control centers and other health organizations use to identify drug products.

Proposed § 208.24(e) would require, in the absence of an exemption under proposed § 208.26, that an authorized dispenser provide a Medication Guide to the patient (or the patient's agent) at the time a prescription drug product is dispensed under a new prescription, and when requested by the patient for refill prescriptions.

Section 510 of the act (21 U.S.C. 360) requires all persons engaged in the manufacture, preparation, propagation, compounding, or processing of a drug to register with FDA and provide the agency with a list of drug products in commercial distribution. Under section 510(g)(1) of the act, however, pharmacies which conform to local laws, which are regularly engaged in dispensing prescription drugs upon prescriptions of licensed practitioners, and which do not manufacture, prepare, propagate, compound, or process drugs for sale other than in the regular course of dispensing drugs at retail, are exempt from the registration and listing requirements. The preparation and/or distribution of Medication Guides by a pharmacy does not diminish this exemption. Accordingly, under proposed § 208.24(f), authorized dispensers are not subject to section 510 of the act solely because of an act performed by the authorized dispenser to comply with this regulation.

F. Exemptions and Deferrals

The regulatory requirements presented in proposed § 208.20 are intended to be exhaustive as to the content of Medication Guides. Nevertheless, FDA realizes that some requirements in proposed § 208.20 may be inapplicable, unnecessary, or contrary to a patient's best interests for a particular drug product. Accordingly, proposed § 208.26(a) would advise manufacturers to contact FDA if they believe that certain requirements are inapplicable, unnecessary, or contrary to the patient's best interest.

Proposed § 208.26(a) would also allow FDA to determine that certain information should be omitted from the Medication Guide for a particular drug product. This determination would occur at the time a Medication Guide was submitted as part of a marketing application. The agency may also, on its own initiative or in consultation with a manufacturer, determine that any or all of the Medication Guide requirements should be deferred or exempted for a specific drug product.

The agency expects that the Medication Guide will facilitate communication between the health professional and patient, thereby enhancing the proper use of prescription drug products and helping to reduce the incidence of noncompliance and adverse reactions. FDA emphasizes, however, that the Medication Guide is not intended to displace or substitute for professional judgment. A practitioner may feel that, in certain cases, a patient may be adversely affected by the contents of a Medication Guide.

Consequently, under proposed § 208.26(b), the authorized dispenser of a prescription drug product would not

be required to provide a Medication Guide to a patient if the licensed practitioner who prescribes the drug product directs that the Medication Guide be withheld. The agency believes that prescribers should not direct dispensers to routinely withhold a Medication Guide from patients but should do so only when it is in the best interests of the specific patient involved.

In addition, FDA believes that authorized dispensers, as a result of their personal contact with a specific patient or a patient's family, often have information relevant to a decision to withhold a Medication Guide for a specific product. For example, an elderly patient functioning at a relatively low level of awareness of his cancer may have been prescribed a product that provides only palliative care, or a schizophrenic patient may have been prescribed a clearly anti-psychotic drug. Under such circumstances, the patient, and the course of therapy, may be adversely affected by the contents of a Medication Guide. Under these circumstances, where there are significant concerns about potential adverse effects of a Medication Guide, FDA would permit authorized dispensers to use their professional judgment in determining whether a particular patient would be best served by withholding the Medication Guide for a particular product. However, such an action should be based on the professional judgment of the authorized dispenser in each specific situation, and Medication Guides should not routinely be withheld for specific drug classes or specific patient characteristics. The agency invites comments on how best to implement this exemption.

FDA notes that under proposed § 208.26(b), the authorized dispenser must provide the Medication Guide to any patient who requests one. In addition, FDA has determined that for particular products patient information should be provided to all patients. Section 208.26(b) therefore provides that this exemption does not apply if FDA determines that a Medication Guide for a particular product should be provided to all patients under all circumstances.

Proposed § 208.26(c) would permit manufacturers, distributors, or authorized dispensers to provide drug products without a Medication Guide in emergency situations and in cases where the manufacturer, distributor, or authorized dispenser has made a good faith effort to obtain a Medication Guide for the drug product, but does not have a Medication Guide available for the patient. The manufacturer, distributor, or authorized dispenser would be required to document its good faith effort to obtain a Medication Guide. This provision is intended to address those situations where the Medication Guide is unavailable and would not prohibit authorized dispensers from providing a prescription drug product to a patient. For example, if an authorized dispenser is utilizing computer-generated Medication Guides and the computer system breaks down, or if an authorized dispenser had exhausted its supply of the Medication Guide for a particular drug product and was unable to secure an additional supply of the Medication Guide, proposed § 208.26(c) would permit the authorized dispenser to provide the drug product to the patient without a Medication Guide.

Proposed § 208.26(d) would exempt certain authorized dispensers from the requirement, in § 208.24(e), to provide a Medication Guide directly to each patient when dispensing a prescription drug product. This proposed exemption would apply to retail pharmacy outlets or other dispensers which: (1) Dispense, on average during the previous calendar year, no more than 300 outpatient prescription drugs per week; (2) have gross annual sales of no more than $5.0 million or are part of a business entity (i.e., sole proprietorship, partnership, or corporation) that has gross annual sales of no more than $5.0 million; and (3) make available to patients a compilation of current Medication Guides for reading in the drug product dispensing area.

FDA is proposing this exemption because it has determined, based on the agency's regulatory impact analysis in section XII. of this document, that the proposed regulation would have a significant economic impact on the operations of many smaller retail pharmacy outlets. Many larger pharmacies—members of chain drug stores and pharmacies in large food/drug combination stores—have computerized systems that can be used in dispensing Medication Guides to patients. Smaller pharmacies, however, will generally need to purchase computer equipment or they will incur costs for lost time and storage space by using preprinted Medication Guides.

This proposed exemption would not apply to drugs dispensed in unit-of-use containers. In this situation, the impact of the proposed regulation on smaller pharmacies would be less because the drug product is individually prepared for the patient by the manufacturer, and already includes the Medication Guide.

In addition, the proposed exemption would not apply when the agency determines, for safety or other reasons, that a particular drug product must be dispensed with a Medication Guide. For example, FDA currently requires that patient labeling must be dispensed with Accutane to ensure its safe use, i.e., to warn patients about its association with birth defects.

Exempted pharmacies must maintain a current compilation of Medication Guides available for consumers to consult in an accessible area, such as near the counter or the patient counseling area.

This proposed exemption is intended to lessen the economic impact of complying with the proposed Medication Guide dispensing requirements for smaller pharmacies and other dispensers. FDA invites general comments on this exemption and specific comments on the proposed threshold level (300 prescriptions per week) and whether this proposed exemption should be permanent or merely extend the time necessary for smaller pharmacies to comply with the exemption, for example by providing a 10-year extension for small businesses to comply with the requirements.

G. Miscellaneous Amendments

The proposed rule would also amend the provisions pertaining to NDA's, product license applications (PLA's) and abbreviated new drug applications (ANDA's) and abbreviated antibiotic drug applications (AADA's) to require applicants to include a Medication Guide as part of their labeling. The agency intends to review the Medication Guide along with the proposed professional labeling for the drug product or review the Medication Guide as it would review any proposed labeling change for a drug product that requires prior approval. Although the Medication Guide program would be implemented gradually if the performance standards are not met, its requirements would ultimately apply to all prescription drug products that patients primarily self-administer without the direct supervision of a health care professional. Therefore, as labeling, the proposed rule would expressly require that the Medication Guide be submitted as part of an NDA, PLA, or ANDA.

For applicants with approved products, the proposed rule would amend the regulations governing supplemental applications to require applicants to obtain prior FDA approval of any change to a Medication Guide. FDA is proposing to require prior approval of such changes, including the addition of any warning or adverse reaction, or even minor editorial

changes. As stated earlier, the Medication Guide is directed to consumers who may be distracted or overwhelmed by excessive information. Consequently, the agency will attempt to ensure that the Medication Guide contains information that consumers should know and can understand.

XI. Legal Authority

The act (21 U.S.C. 321 *et seq.*) authorizes FDA to regulate the marketing of drug products so that the products are safe and effective for their intended uses and are properly labeled. In order to carry out the public health protection purposes of the act, FDA: (1) Monitors drug manufacturers and distributors to help make certain that drug products are manufactured and distributed under conditions that ensure their identity, strength, quality, and purity; (2) approves new drugs for marketing only if they have been shown to be safe and effective; and (3) monitors drug labeling and prescription drug advertising to help ensure that they provide accurate information about drug products.

A major part of FDA's efforts regarding the safe and effective use of drug products involves FDA's review, approval, and monitoring of drug labeling. Under section 502(a) of the act (21 U.S.C. 352(a)), a drug product is misbranded if its labeling is false or misleading in any particular. In addition, under section 505(d) and (e) of the act (21 U.S.C. 355(d) and (e)), FDA must refuse to approve an application and may withdraw the approval of an application if the labeling for the drug is false or misleading in any particular.

Section 201 of the act (21 U.S.C. 321), the ''Definitions'' section of the act, describes the concept of ''misleading'' in the context of labeling and advertising. Section 201(n) of the act (21 U.S.C. 321(n)) explicitly provides that in determining whether the labeling of a drug is misleading, there shall be taken into account not only representations or suggestions made in the labeling, but also the extent to which the labeling fails to reveal facts that are material in light of such representations or material with respect to the consequences which may result from use of the drug product under the conditions of use prescribed in the labeling or under customary or usual conditions of use.

These statutory provisions, combined with section 701(a) of the act (21 U.S.C. 371(a)), clearly authorize FDA to promulgate a regulation designed to ensure that patients using prescription drugs will receive information that is material with respect to the consequences which may result from the use of a drug product under its labeled conditions. This interpretation of the act and the agency's authority to require patient labeling for prescription drug products has been upheld. (See *Pharmaceutical Manufacturers Association* v. *Food and Drug Administration,* 484 F. Supp. 1179 (D. Del. 1980), *aff'd per curiam,* 634 F. 2d 106 (3rd Cir. 1980)).

For generic drug products, section 505(j)(2)(A)(v) of the act (21 U.S.C. 355(j)(2)(A)(v)) provides additional legal authority for a Medication Guide. Section 505(j)(2)(A)(v) of the act requires an ANDA to contain information to show that the proposed generic drug product's labeling is the same (with some exceptions) as that of the corresponding reference listed drug. Thus, because a Medication Guide is drug labeling, FDA proposes to require generic drug product manufacturers to develop a Medication Guide that is the same as the one for the reference listed drug, except for differences attributable to legal or regulatory requirements (such as uses protected by patent) or because the generic drug product and the reference listed drug are produced or distributed by different manufacturers. If an ANDA or AADA fails to contain such information, this failure may be grounds for refusing to approve the ANDA or AADA under section 505(j)(3)(G) of the act (21 U.S.C. 355(j)(3)(G)).

In addition, for biological products, section 351 of the Public Health Service Act (42 U.S.C. 262) authorizes the imposition of restrictions through regulations ''designed to insure the continued safety, purity, and potency'' (including effectiveness) of the products. Biological product licenses are to be ''issued, suspended, and revoked as prescribed by regulations'' (42 U.S.C. 262(d)(1); see 21 CFR 601.4 through 601.6). The requirements of this proposed regulation on Medication Guides are designed, in part, to insure the continued safe and effective use of licensed biological products. Therefore, the agency may refuse to approve PLA's, or may revoke already approved licenses, for biological products that do not comply with the requirements of the final rule on Medication Guides.

Based upon these authorities, the agency proposes to require manufacturers of prescription drug products, including biological products, to disclose information about their products in the form of patient labeling. Just as scientific standards for evaluating a drug product's safety and effectiveness and manufacturing practices have evolved since enactment of the act in 1938, standards for appropriate labeling for drug products must also change as data are compiled about the effects of labeling on patients' safe and effective use of drug products.

XII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–345). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the principles set out in the Executive Order.

The distribution of useful patient information will result in significant consumer benefit, but may also entail costs to industry. Some of the regulatory alternatives examined by the agency entail potential regulatory costs well in excess of $100 million. Even though the selected option is estimated to have associated costs well below this amount, FDA has prepared a preliminary economic analysis in accordance with Executive Order 12866 and the Regulatory Flexibility Act.

This preliminary economic analysis evaluates the costs and benefits of implementing FDA's proposal. This proposal states that in the absence of continued voluntary efforts to provide useful information to patients who purchase prescription drug or biological products, manufacturers of these products will be required to prepare and distribute patient information labeling that will accompany any new prescriptions. The objective of the proposed rule is to improve public health by allowing patients to make more informed uses of their medications. FDA has found that patients often fail to adhere to medication regimens or to recognize signs and symptoms of both preventable and unpreventable adverse drug reactions. These failures frequently prolong recovery or even contribute to additional illnesses. Because patients who receive understandable information about their drug therapies are better able to benefit from their medications, FDA believes that implementation of the proposed regulations will significantly enhance the public health. Although many programs that offer patient prescription drug information currently exist, this proposal is expected to increase the use and quality of such information, and provide standards for

guiding and assessing the adequacy of voluntary programs.

FDA has proposed to institute a comprehensive program of FDA-approved patient information only if the private sector does not meet defined goals for the distribution and adequacy of patient information. These goals are both reasonable and attainable. It is FDA's hope that the voluntary programs will achieve the desired goals and that consequently a government-imposed program will not be required. However, this was FDA's hope in 1982 when the initial PPI regulations were withdrawn. To provide sufficient incentive to meet distribution and quality goals for written patient information, FDA is proposing two alternatives that could result in a comprehensive program requiring FDA-approved Medication Guides, but no sooner than 5 years from the effective date of the final rule.

To estimate the costs of such a regulation, we have prepared a worst-case analysis that assumes no increase in the current state of distribution and quality of dispensed patient information, assumed to be at about 50 percent. This worst-case estimate is that the program would have annual gross costs of approximately $56 million, assuming neither inflation nor discounting. Thus, FDA estimates that the cost of this regulation would range from zero (if distribution and quality standards would have been achieved despite the promulgation of this rule) to $56 million (if the current state of private sector issuance of patient information would have remained unchanged.)

The proposed labeling would take the form of patient information sheets, called Medication Guides. These sheets would accompany new prescriptions for outpatient human drug and biological products, and would also be available upon request for refill prescriptions.

If the regulation is implemented, Medication Guides would be developed by drug manufacturers. They would be approved by FDA and would contain information designed to increase patient awareness of the proper use of the accompanying products. These information sheets would be distributed to the patient at the time the prescription is dispensed at the retail pharmacy (or other dispensing outlet). While manufacturers would be responsible for ensuring that adequate information is available to the dispenser, the dispenser would ultimately provide the information to the patient at the time the prescription is filled. The agency has taken the burden of small, retail pharmacies into account, and exempted certain low-volume outlets from this proposal.

In 1980, the agency issued a similar regulatory proposal calling for PPI's, initially to cover 10 drugs and drug classes. That rule was revoked in 1982 to permit the private sector to implement information programs without Government intervention. In the intervening years, FDA has conducted periodic surveys of patients who have obtained new prescriptions. FDA found in the latest survey that the proportion of patients receiving written drug information (other than the prescription label on the container) had increased from 16 percent in 1982 to 58 percent in 1994. Preliminary analyses of FDA's most recent survey indicate that 55 percent of patients obtain more substantial information than brief stickers.

Other surveys of the pharmacy sector have also shown gains in distribution of written information. A 1992 survey of retail pharmacies conducted by the University of Mississippi showed that 77 percent of all pharmacies distribute printed patient counseling information (Ref. 76). A 1994 Consumer Patient Counseling Survey conducted for the National Association of Boards of Pharmacy (Ref. 95) showed that 64 percent of all patients or caregivers stated that they received printed materials about the medication from the pharmacy.

The agency believes that the availability of patient information should continue to grow. While there is little doubt that patient information activities have increased since the 1980 PPI proposal, a sizeable proportion of the patient population remains underinformed. FDA believes that a regulatory process that encourages or augments private sector initiatives will best meet the needs of these underserved patients.

OBRA '90 currently requires that pharmacists offer counseling to patients who receive State-assisted services. Many States have extended OBRA's requirements to additional patients. Required counseling under OBRA is limited to oral, face-to-face counseling between the patient and the dispensing pharmacist. Written material may be used as an adjunct, but cannot be substituted for oral counseling. Numerous studies have shown that counseling is most effective in modifying behavior when achieved through a combination of oral and written media. Thus, FDA believes that Medication Guides, or other voluntary written information, will complement OBRA requirements and provide more effective and comprehensive patient counseling.

A. Affected Sectors

The economic effects of the proposed regulations, if implemented, will vary with the number of affected drug products, prescriptions, and retail pharmacies. The number of affected drug products will dictate the number of separate Medication Guides that will be developed, the number of prescriptions will dictate the number of Medication Guides that will be distributed, and the number of pharmacies will dictate the number of facilities that will maintain equipment to distribute Medication Guides. To determine an initial baseline for this analysis, the discussion that follows is based on the assumption that voluntary information programs will not meet the distribution and quality standards for voluntarily-supplied patient information, and that the Medication Guide program will therefore be fully implemented.

Medication Guides must be available for most prescription drug and biological products dispensed outside of institutional environments (such as hospitals and nursing homes). The agency envisions an implementation period of 10 years, so that early resources may be spent developing Medication Guides for therapies that may pose public health concerns, as well as for new products. Over time, however, this analysis assumes that all prescription products that are the subject of approved NDA's and ANDA's will be accompanied by Medication Guides. FDA examined currently marketed drug products and their historical rates of introduction to arrive at an estimated 3,350 separate drug products that will require separate Medication Guides, as shown in Table 1.

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Table 1

Numbers of Drug Products, Prescriptions, and Resultant Medication Guides

	Number
Model Products	461
Category Products	782
Generic Products	2,107
Guides Developed	3,350
	Number (in millions)
Total Prescriptions	2,186
Unit-of-Use Prescriptions	525
Pharmacy Prepared Prescriptions	1,661
Pharmacy Prepared New Prescriptions	914
Requested Refill Guides	83
Guides Dispensed	1,522

Sources: Drug Products from FDA Data
Prescriptions from NACDS; 1992

The 3,350 drug products will eventually require separate Medication Guides. To develop these, FDA estimates that companies will select ''models'' from already existing materials. These models would be updated by the manufacturer. Once a manufacturer has developed a model it would be submitted to FDA for approval. The approved Medication Guide will then serve as a model for other similar drugs within the same therapeutic category, saving additional developmental costs. FDA analysis indicates that 461 guides will serve as ''innovator'' or ''model'' Medication Guides. These can serve as models for 782 similar ''category'' products (within narrowly-defined therapeutic categories) which, in turn, can be copied on a word-for-word basis for 2,107 generic drugs.

About 2.2 billion prescriptions were dispensed from retail pharmacies during 1992, according to data included in the ''Prescription Drug Marketing Simulation Model'' developed by the NACDS (Ref. 75). The proposed regulation, if fully implemented, will require Medication Guides to accompany each new prescription, as well as be available upon request for refill prescriptions. For cost calculation purposes, FDA has assumed that prescriptions dispensed via unit-of-use packaging would include Medication Guides whether the prescriptions are new or refills. Since approximately 24 percent of all prescriptions, or 525 million prescriptions, are issued in unit-of-use packages, an additional 1,661 million prescriptions would need to be prepared by a pharmacist. Of these, FDA estimates that approximately 55 percent, or 914 million, would be for new prescriptions. FDA also estimates that 5 percent of the 1,661 on-site, pharmacy-prepared prescriptions, or 83 million, would be for patient requests for Medication Guides for refill prescriptions. Thus, as shown in Table 1, the agency estimates that if the proposal were fully implemented, Medication Guides would be issued for 525 million unit-of-use prescriptions, 914 million other new prescriptions, and 83 million refill prescriptions, for a total of 1,522 million Medication Guides. This would cover 70 percent of all prescriptions.

However, pharmacies consist of both commercial and noncommercial outlets. The NACDS (Ref. 75) included a distribution of pharmacy outlets by type. The agency has allocated these outlets into three categories: Independent pharmacies (up to three outlets that fill prescriptions), chain pharmacies (four or more outlets under the same management, including food outlets and mail-order companies), and noncommercial outlets (Health Maintenance Organizations (HMO's)), hospitals, ambulatory care units, and physician offices), as shown in Table 2. Average prescription volume by outlet type is derived from the NACDS survey. Independent, community pharmacies are estimated to average approximately 530 prescriptions per week, while an average chain pharmacy averages over 825 weekly prescriptions. Overall, the agency estimates that the typical pharmacy dispenses approximately 600 prescriptions per week.

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Table 2

Retail Outlets and Prescription Volume

	Number of Outlets	Annual Prescriptions (In Millions)	Percent Prescriptions	Average Weekly Prescriptions
Independent Outlets	32,499	896.4	41.0	530
Traditional Chains	20,193	791.5	36.2	754
Food/Drug Combos	4,291	153.0	7.0	686
General Merchandise	2,688	94.0	4.3	672
Deep Discounters	903	39.4	1.8	839
Mail Orders	34	131.2	6.0	74,208
Sub-Total -- Chains	28,109	1,209.1	55.3	827
SUB-TOTAL COMMERCIAL	60,608	2,105.5	96.3	668
HMO's	1,179	21.9	1.0	357
Hospitals	1,080	17.5	0.8	312
Physician Offices	5,500	28.4	1.3	99
Ambulatory Centers	3,000	13.1	0.6	84
Sub-Total -- Others	10,759	80.9	3.7	145
TOTAL OUTLETS	71,367	2,186.4	100.0	589

Source: NACDS; 1992

B. Gross Costs of Compliance

FDA estimated the regulatory costs of this proposed regulation by developing the costs for dispensing Medication Guides at a typical (600 prescriptions per week) pharmacy. These costs were divided by the number of dispensed Medication Guides to derive a cost per Medication Guide, as well as multiplied by the number of outlets to derive a total cost of compliance. While this methodology may overstate unit costs for large outlets and understate unit costs for small outlets, due to economies of scale, these effects would tend to balance in the aggregate.

Because voluntary efforts exist to provide patient information, and these efforts are expected to expand, the incremental costs of compliance are only those above the costs of providing patient information that would accrue in the absence of this proposal. The agency has initially assumed that 50 percent of all patients currently receive patient information. Thus, gross costs are reduced to account for current activities. If private sector initiatives continue to grow in the absence of this regulation, the actual incremental compliance costs will be even further reduced. In fact, if all affected pharmacies would voluntarily dispense adequate, written patient information, the incremental costs of this proposal would be zero. However, to develop a baseline for analysis, the agency has assumed that the current baseline of 50 percent compliance will remain constant throughout the study period. This strategy results in the most conservative (i.e., the highest possible) estimate of costs.

Costs to manufacturers include the cost of developing Medication Guides and submitting them for FDA review. Costs to pharmacies include the cost of printing and dispensing Medication Guides with prescriptions.

1. Manufacturers

The worst-case scenario would require manufacturers of new drugs to develop Medication Guides with no prior model or prototype, for example, for a newly approved drug in a new therapeutic class. According to Merck Pharmaceuticals, it took 6 months of calendar time to develop, test, and revise an FDA-approved PPI to accompany a recent new drug. FDA assumes that a totally new Medication Guide could be developed within this timeframe, and would require a total of 2 months of full-time effort by manufacturers. This effort would include scientific research associates, regulatory affairs officials, and legal/scientific reviewers. Assuming an annual average professional labor cost of $70,000, each model Medication Guide would cost industry between $11,000 and $12,000.

The majority of Medication Guides (those for which there are models in the same therapeutic class) would be very similar to their applicable model guides in content. FDA expects that the cost for developing these ''category'' Medication Guides should be less than half of the model development cost, or approximately $5,000.

Medication Guides for generic drugs should be virtually identical to the originator product's Medication Guide, except for the name, description, and patent-protected information. Therefore, FDA estimates that the cost of developing generic Medication Guides would be approximately one-tenth the cost of developing a category Medication Guide, or $500.

Total industry costs of developing Medication Guides, if voluntary efforts do not continue to grow, are found by multiplying the applicable development cost by the expected number of products shown in Table 1. By the 10th year of implementation, all products would have Medication Guides at a cost to industry of approximately $10.5 million for development. Given the proposed phase-in plan, the agency expects annual development costs to equal approximately $1.3 million by year 10. As new products continue to be marketed, FDA expects this equilibrium to be maintained.

According to data developed by FDA, approximately 24 percent of all prescriptions are dispensed in unit-of-use packaging. These prescriptions would require preprinted Medication Guides that would likely be included in the packaging provided by the manufacturer prior to shipping. Thus, 525 million preprinted Medication Guides will be required by the 10th year of implementation.

According to purchasers, the cost of preprinted patient information sheets is currently about $0.025 per page. These sheets include customized information such as company address, phone numbers, logo, and other information. A supplier of patient information sheets (USP) lists a price of $2.10 for a pad of 50 sheets ($0.042 per sheet), but the order form provides for substantial discounts for bulk orders. FDA has assumed a cost of $0.025 per preprinted patient information sheet, for a total annual printing cost of $13.1 million. The agency believes that current packaging technology would allow for insertion of Medication Guides into unit-of-use packaging with little additional cost.

Prescriptions in other than unit-of-use packaging will likely be dispensed with Medication Guides that are generated at the retail pharmacy via computer. Many of the technologies for transmitting automated information to retail pharmacies are already in place. Distributor-based electronic information networks offer nationwide computer ties designed to influence as well as facilitate pharmaceutical care. According to one industry analyst, ''Nearly 95 percent of all pharmacies in the U.S. have at least some computer link to a point-of-sale system that allows them to participate in these point-of-sale networks.'' (Ref. 73).

Although a precise prediction of future technologies remains speculative, FDA believes that the current availability of computers in almost all pharmacies indicates that patient information would be available in an automated format.

A number of possibilities would be available for the distribution of automated data to pharmacies. Although each individual manufacturer could distribute data disks to all pharmacies purchasing their drugs, this approach would entail routine shipments of hundreds of thousands of data disks and require expensive recordkeeping systems to avoid sending duplicate disks. It is far more likely that conventional market forces would lead to more rational information systems.

Logical models for distributing computerized information data bases include the third parties that already accumulate and disseminate these data. Because the regulation will impose the initial responsibility for information distribution on manufacturers, yet the pharmacies will need to augment their computer systems, the precise outcome of these market forces is uncertain. However, there are several reasons to believe that competitive considerations would prompt manufacturers to coordinate with third party data bases for the distribution of Medication Guides.

First, several vendors, such as the USP, Medi-Span, Inc., and the ASHP, already provide computerized drug information data bases. Thus, comparable systems are already in place. Second, the responsiveness of the private sector to the demand for Government-mandated information has been vividly demonstrated by the proliferation of vendors of chemical data bases following the promulgation of the Occupational Safety and Health Administration's ''Hazard Communication Standard.'' Finally,

pharmaceutical manufacturers would vigorously support the development of a data distribution network that reduces the costs of printing and shipping large volumes of paper. The initial mechanism could reasonably involve manufacturer price discounts, rebates, or other like incentives designed to encourage pharmacies to use commercial data bases.

For this preliminary study, the costs of disseminating computerized data are considered pharmacy costs, via the purchase of software and updates, although part of this burden may be passed back to the manufacturers or distributors through various incentive programs. Table 3 indicates that the total annual gross costs to manufacturers of preparing Medication Guides and printing those used in unit-of-use packages would be expected to reach $14.4 million, if the proposed regulation is fully implemented.

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Table 3

Gross Annual Compliance Costs for Manufacturing and Pharmacy Sectors (Millions of Dollars)

	Manufacturers Cost	Pharmacy Cost	Total Annual Cost	Percent of Annual Cost (%)
Guide Development	1.3		1.6	1
Printing Unit-of-Use	13.1		13.1	11
Computer Hardware		6.6	6.6	5
Computer Supplies		27.4	27.4	23
Computer Software		22.5	22.5	19
Storage		7.4	7.4	6
Time		42.8	42.8	35
Total	14.4	106.7	121.1	100

2. Pharmacies

FDA has estimated the costs for a typical pharmacy that dispenses 600 prescriptions per week to comply with the proposed regulation. These costs include hardware (including a computer with sufficient hard disk space and a dedicated printer), supplies, space, and time to retrieve and dispense the Medication Guide.

a. *Hardware.* An estimate of the required hard disk space to operate a drug information network was developed from current requirements of the MEDTEACH program offered by ASHP, which provides 427 drug monographs to customers in disk form (each monograph contains information similar to that envisioned in a Medication Guide). The installation program requires two disks and quarterly updates or revisions are offered to all users.

ASHP reports that the current program and data require 3.1 megabytes of hard disk space. A program accounting for 1,000 monographs would require 6 megabytes. Because the proposed regulations, if implemented, would require 3,350 specific Medication Guides, the required disk space would ultimately be almost 20 megabytes. Hard disks exceeding 400 megabytes are now common at a price of under $1.00 per megabyte, and the technology is steadily advancing. FDA foresees no difficulty in meeting the longer term requirements for computer disk space, at an average amortized annual cost of only $6.

Dedicated printers would be required to generate the large numbers of Medication Guides. Dot matrix printers can be purchased for about $300, and are assumed to have a useful life of 4 years, which results in an amortized cost per printer of $87 per year (at 6 percent interest). Laser printers are assumed to cost $1,000 and also have a 4-year useful life, yielding an amortized annual cost of $289 per printer.

FDA found that the relatively slower dot-matrix printers would be adequate for most outlets. The dispensing clerk or pharmacist would complete other filing or labeling activities while the printer was operating.

b. *Supplies.* On the assumption that each computer-generated Medication Guide would fill two pages, FDA estimates that dot-matrix printers would require ribbon replacement every 1,250 pages, or 625 Medication Guides. Dot-matrix ribbons are estimated to cost $8. In addition, office supply catalogs indicate that the cost of bulk computer paper ranges from less than $0.005 to $0.01 per page. This study uses $0.007 per page as a mid-point in this range for a cost of $0.014 per 2-page Medication Guide.

A typical pharmacy is estimated to dispense 600 prescriptions per week. Twenty-four percent of these prescriptions (144) are dispensed in unit-of-use packaging, so a total of 456 prescriptions per week may require site-generated Medication Guides. The proposed regulation requires Medication Guides to accompany new prescriptions (55 percent of the total) as well as be available upon request. Thus, 60 percent of the affected prescriptions are expected to be accompanied by Medication Guides. This represents about 275 per week, or 14,300 per year when fully implemented.

The typical pharmacy would then require 23 ribbon replacements per year (almost one ribbon every 2 weeks) for an annual cost of $184. In addition, 28,600 pages of computer paper would cost a pharmacy $200 per year. The gross annual cost of supplies for providing Medication Guides at a typical pharmacy is therefore estimated to equal $384.

c. *Software.* Several companies, including the USP and ASHP, currently sell computerized patient information disks to pharmacies. Although these packages have limited coverage, and typically contain data for only the 200 top-selling drugs, FDA believes that such organizations could rapidly compile and market comprehensive Medication Guide data bases. Based on current costs for these software and data packages, this study assumes an initial cost of $400 and quarterly updates of $50 each. When these costs are amortized over a 4-year period, the resultant annual cost to the pharmacy equals $315.

d. *Storage.* Using computers to print Medication Guides would also add costs for storage, because an additional printer and paper would require approximately 2 square feet within the prescription preparation area. For example, 1,000 sheets of paper may be stored in a stack of only 1.5 inches. Storage space would still be available below the preparation counter, so FDA assumes that potential displacement of equipment would be equal to 1 square foot of floor space.

The conventional means of obtaining the economic cost of a productive resource is to estimate the market price of that resource. An annual rental charge of $7.50 per square foot of pharmacy space was obtained from survey data contained in the 1992 Lilly Digest (Ref. 78). Alternative approaches note that, in the short run, added storage requirements could impose additional opportunity costs if the turnover of goods could not be increased elsewhere in the pharmacy, which suggests a cost of storage based on displaced sales. FDA believes that this method likely overstates regulatory costs, both from a societal perspective (because the loss in sales to any one outlet would be gained by another) and an individual outlet perspective (because the average return per square foot of space exceeds the marginal return). That is, outlets would minimize any burden by displacing lower return items. Nevertheless, FDA has derived the value of sales per square foot from the 1992 Lilly Digest of independent pharmacies, and has used an annual cost of $104 per pharmacy per square foot to account for annual storage costs to the typical pharmacy. (Annual sales per square foot of pharmacy equal $360, and pharmacies have an average 29 percent gross sales margin. Thus, $360 × .29 = $104).

e. *Time.* Computerized pharmacies would incur relatively low burdens of time, because Medication Guides would be printed as other labeling and dispensing activities were occurring. However, pharmacists would remain responsible for ensuring that the correct Medication Guide accompanies each prescription. FDA has assumed that a minimum of 5 seconds of pharmacist time would be needed to verify each selection. Since the annual number of Medication Guides per typical pharmacy would equal 14,300, a pharmacist would be expected to spend almost 20 hours per year verifying Medication Guides.

The 1992 Lilly Digest reported average hourly wage rates of $30 for pharmacist/proprietors. Using this as a basis, the total annual cost of time would equal $600 for the typical pharmacy.

Although it is possible that this patient information would cause returns of drugs and additional questions of pharmacists, FDA is unaware of any study that confirms this hypothesis. The agency's 1980 economic analysis cited a contracted survey that indicated that no additional pharmacist time was required to address these concerns (Ref. 62). FDA invites additional public comment and data on more recent experience.

f. *Total compliance costs to pharmacies.* The sum of the annual costs of printers, supplies, software, storage, and time equal almost $1,500 for the typical pharmacy when, and if, the proposed regulations are fully implemented. This equals almost $0.105 per pharmacy-printed Medication Guide. Table 3 contains the total gross annual costs for the pharmacy sector.

Total annual gross costs to the retail pharmacy sector will equal $106.7

million if this regulation is fully implemented. This amount is found by multiplying the cost per pharmacy by the 71,367 universe of outlets shown in Table 2.

3. Total Annual Gross Costs of Developing and Dispensing Medication Guides

The estimated annual gross costs of developing and issuing Medication Guides include the annual costs to manufacturers of developing Medication Guides, in general, and printing unit-of-use Medication Guides ($14.4 million), and the total annual cost to retail pharmacies of printing and dispensing Medication Guides ($106.7 million). Thus, the total gross annual compliance cost of this proposal is estimated to equal $121.1 million. The estimated average cost to distribute one Medication Guide, whether via unit-of-use packaging or printed at a retail pharmacy, equals $0.08. This reflects the higher cost of printing Medication Guides on-site as well as the lower cost of including Medication Guides with unit-of-use packaging.

This estimate does not take into account the existence of current voluntary patient information programs. It also assumes static technologies and prescription demand.

C. Incremental Compliance Costs

As discussed earlier, the agency has assumed that current voluntary programs account for 50 percent of the market. Such programs include retail pharmacies that currently provide patient information, manufacturers that provide mandated patient information for certain individual drug products and product classes, mail-order pharmacies that routinely provide this information, and general unit-of-use packaging. Given the current state of patient information, the agency expects that the cost of achieving compliance with this proposal, if no further gains in patient information occur, would be only 50 percent of the total gross costs. Thus, the annual incremental cost of this proposal is estimated to be a maximum of $60.5 million (including those Medication Guides dispensed in unit-of-use packages). If private patient information programs continue to increase, on their own, the incremental cost of any regulatory plan would be even lower. In addition, this estimate does not account for the agency's proposal to allow an exemption for small-volume pharmacies. The cost implications of this exemption are discussed in the following section.

D. Small Pharmacy Exemption

The Regulatory Flexibility Act requires Federal agencies to prepare a regulatory flexibility analysis if a proposed regulation is expected to have a significant impact on a substantial number of small entities. FDA believes that compliance with the requirements for Medication Guides could have a significant impact on the operations of many small, independent pharmacies. The agency therefore proposes to exempt from most of the Medication Guide requirements any retail outlet that dispenses an average of fewer than 300 prescriptions per week, as long as total company annual sales do not exceed $5.0 million.

1. Disproportionate Costs

Although pharmacies that dispense the largest volumes of prescriptions would incur the greatest absolute costs, small pharmacies would bear a proportionally higher burden. Based on the assumptions previously discussed, for a typical outlet dispensing 600 prescriptions per week, the average gross cost to provide a Medication Guide is $0.105. The cost for a small outlet dispensing only 200 prescriptions per week would total about $0.177. This disparity reflects the ability of larger outlets to spread the fixed annual regulatory costs (printer, storage, and software) over more prescriptions.

In some circumstances, regulatory costs can be imposed without inflicting noticeable change to the affected industry sectors. However, in recent years, independent community pharmacies have faced rapidly growing competitive pressure from new sources of retail prescriptions, especially mail-order companies and HMO's. A 1992 study prepared for the NACDS (Ref. 75) projected independent pharmacy's share of prescriptions to decrease from 41 percent to 29 percent during the 1990's. IMS America (Ref. 77) reports that since 1990, the number of independent retail pharmacies decreased by 15 percent.

In general, the profitability of retail pharmacies varies in direct proportion to sales volume. For example, a survey of independent pharmacists (Ref. 78) reports that a typical independent pharmacy earned income (combined pretax net store profit and proprietor/manager salary) of $88,000 during 1991. Figure 1 shows that very small independent pharmacies (fewer than 150 prescriptions per week) earned total pretax incomes of only 26 percent of the industry average. Independent pharmacies dispensing between 150 and 300 prescriptions per week earned total income of only 51 percent of the industry average. These limited profits suggest that it would be difficult for small outlets to finance additional regulatory costs.

FDA is aware of the economic problems of the small retail pharmacy and is reluctant to impose additional economic burdens on this sector. Since scant public health benefits would be lost by excluding the smallest pharmacies from the requirement to dispense Medication Guides, the agency proposes exempting these pharmacies from the proposed regulation.

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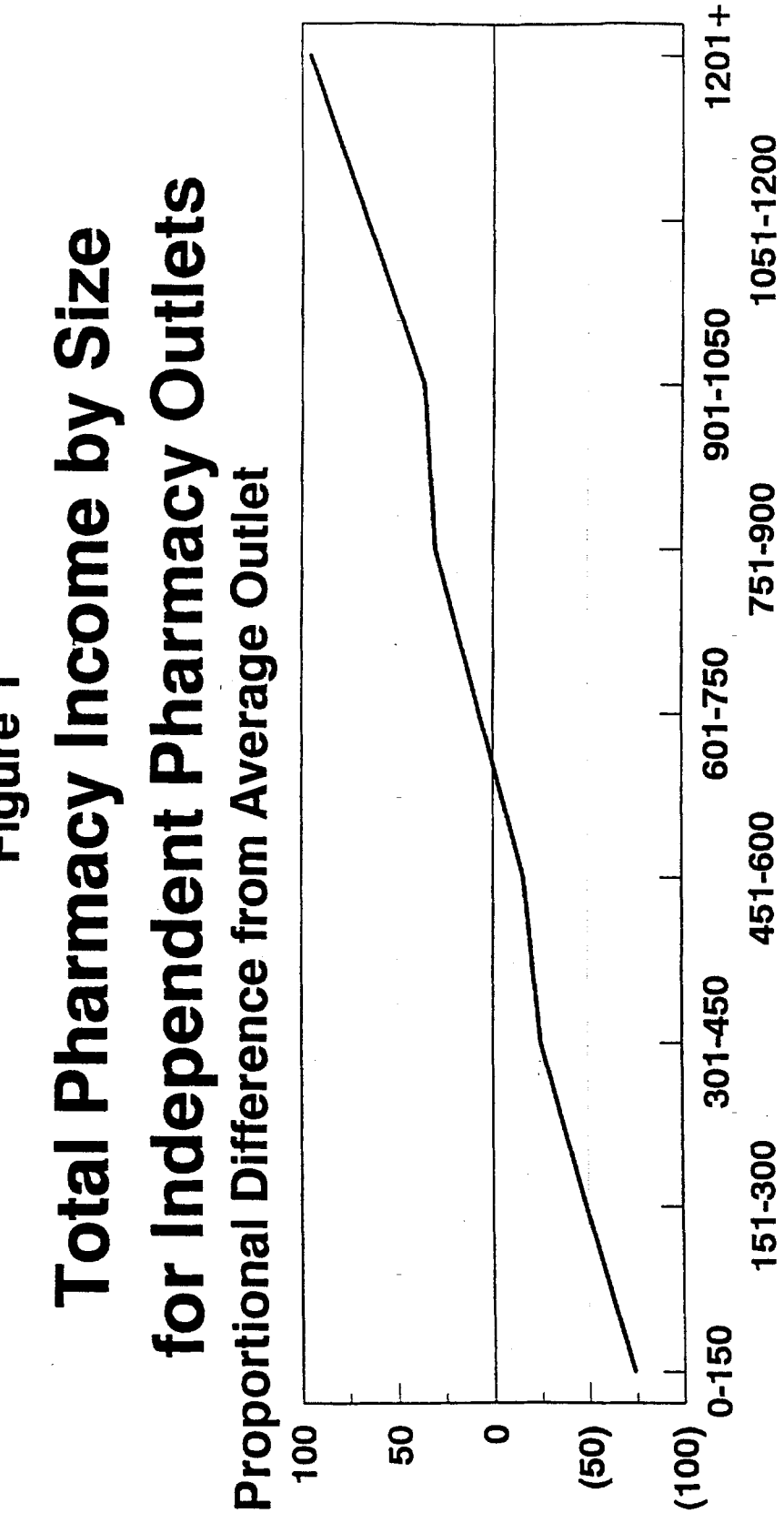
Figure 1

Total Pharmacy Income by Size for Independent Pharmacy Outlets



Income equals net store profit plus salary of proprietor/manager. Source: 1992 Lilly Digest

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2. Outlet Characteristics

To estimate the number of outlets that would be eligible for a small business exemption, FDA constructed a distribution of retail pharmacy outlets by prescription volume. This distribution was developed by merging data from two main sources: the 1992 Lilly Digest of Independent Pharmacies (Ref. 78) and an earlier NACDS study (Ref. 79). Although the Lilly Digest reported data for a self-selected sample of independent pharmacies, it provides the most detailed data available for that sector. The NACDS sampled all pharmacies with six or more outlets. Data are shown in Table 4.

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Table 4

Distribution of Pharmacy Outlets

By Dispensed Prescriptions per Week

	Number of Independents	Number of Chains	Sub-total–Number Commercial	Number of Others	Total Outlets
1-100	715	254	969	4,363	5,332
101-200	2,730	965	3,695	4,431	8,126
201-300	5,070	1,775	6,845	271	7,116
301-400	5,427	2,811	8,238	1,129	9,367
401-500	4,745	2,948	7,693	271	7,964
501-600	3,315	2,621	5,936	181	6,117
601-700	2,372	2,656	5,028	113	5,141
701-800	1,787	2,453	4,240	0	4,240
801-900	1,040	2,110	3,150	0	3,150
901-1000	975	1,933	2,908	0	2,908
1001-1100	975	1,630	2,605	0	2,605
1101-1200	910	1,331	2,241	0	2,241
1201+	2,438	4,622	7,060	0	7,060
Total	32,499	28,109	60,608	10,759	71,367

Independent data from 1992 Lilly Digest
Chain data (incl. other commercial) from NACDS

Because the methodology of these studies varied, FDA standardized the data by adjusting and interpolating between ranges to develop an outlet size distribution for the entire retail sector. The three defined categories of retail outlets were analyzed separately:

Independent Outlets—The 1992 Lilly Digest of independent pharmacies reports prescription volume in terms of prescriptions per day. FDA assumed that pharmacies were open an average of 12 hours a day, and calculated the dispensing days per week from reported weekly hours of operation per cohort. The establishments were then interpolated into cohorts of 100 weekly prescriptions.

Chain Outlets—A distribution of chain outlets was constructed from a May 1990 report entitled ''An Assessment of Chain Pharmacies' Costs of Dispensing a Third Party Prescription'' (Ref. 79) prepared for the NACDS. This report sampled all pharmacies with six or more outlets (including food/drug combinations, general merchandisers, discounters, etc.) and presented a volume distribution by units of annual prescriptions. The agency divided annual prescriptions by 52 to arrive at weekly rates, and again interpolated into cohorts of 100 weekly prescriptions. For the purposes of this analysis, mail-order pharmacies were considered chain outlets.

Other Outlets—Estimates for prescription volumes for other outlets were constructed separately. Hospitals and HMO's reported average weekly prescriptions of approximately 350 per week. Physician's offices and ambulatory care units averaged approximately 100 prescriptions per week. While outlets in this category account for 15 percent of all outlets, they account for less than 4 percent of all prescriptions, and most of these are distributed in unit-of-use packaging. The agency considers this sector to be minimally affected by this proposal and did not analyze its characteristics in detail.

Thus, the agency considered the small business impact on the 60,608 commercial, retail outlets that dispensed about 2.1 billion prescriptions per year. Approximately 54 percent of these outlets are independent while 46 percent are chain outlets.

Figure 2 illustrates the relationship between prescription volume and volume market share, and it shows that outlets dispensing 300 or fewer prescriptions per week account for almost 20 percent of all outlets. However, their dispensed prescriptions account for fewer than 6 percent of all prescriptions.

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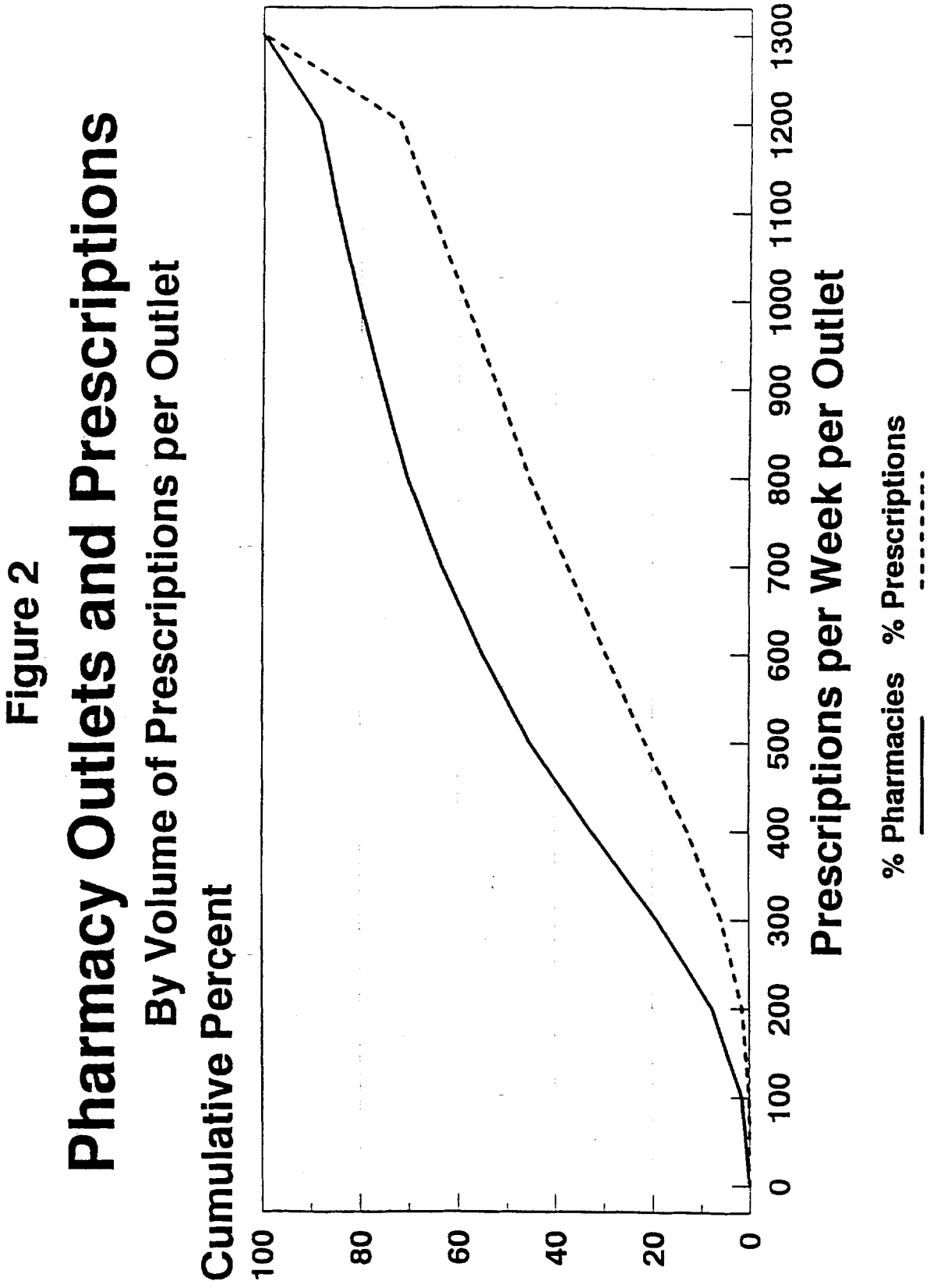

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3. Independent Outlets and Chain Outlets

Independent outlets are typically smaller than chain outlets. As indicated in Figure 3, over 2 percent of all independent pharmacies dispense fewer than 100 weekly prescriptions, while only 0.9 percent of all chain outlets are so small. Conversely, about 7.5 percent of all independent outlets dispense more that 1,200 weekly prescriptions while almost 17 percent of all chain outlets are that large. This results in chain outlets accounting for 26 percent of all outlets with fewer than 100 weekly prescriptions, but 66 percent of all outlets dispensing more than 1,200 weekly prescriptions.

Moreover, chain outlets earn more store revenue on nonpharmacy items. An annual survey conducted by the Drug Store News (Ref. 80) shows that prescription sales account for only 24 percent of total store sales in chain outlets, but 64 percent of sales in independent outlets. In comparison, a typical independent outlet that dispenses fewer than 300 weekly prescriptions has average annual gross revenues of less than $300,000. A typical chain outlet that dispenses the same number of prescriptions will have gross revenues of over $1 million. As the average chain operates 47 separate outlets, these data suggest that very few chain outlets would be eligible for the small business exemption.

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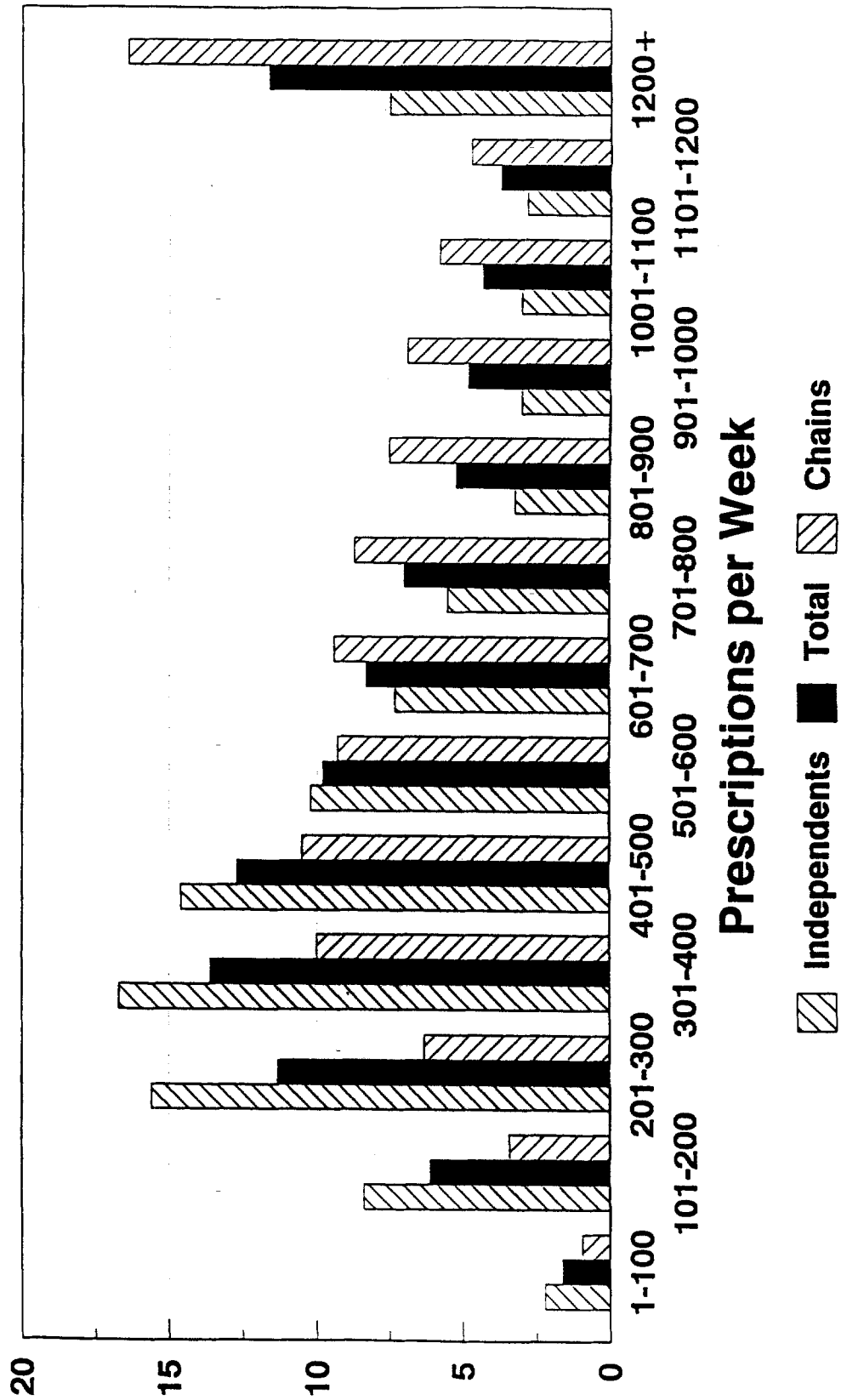
Figure 3



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4. Impact of Small Pharmacy Exemption

FDA proposes to exempt small pharmacies from the Medication Guide requirements if three conditions are met. The first two conditions are based on outlet characteristics. Based on distributions of prescription volume, a proposed outlet size limit of 300 prescriptions per week would exempt about 19 percent of all commercial pharmacies. However, the objective of the exemption is to minimize burdens on small business. Thus, company size, rather than outlet size alone, must be considered. FDA has adopted the Small Business Administration's limit of $5.0 million in annual company sales as an additional criterion for exemption. Thus, an outlet that is a subsidiary of a company with total sales of more than $5.0 million, regardless of sales at the specific outlet, would not qualify for the exemption.

Given these two criteria, FDA estimates that the proposed exemption would cover about 14 percent of all commercial outlets, primarily independent pharmacies. Altogether, these pharmacies dispense only about 4 percent of all prescriptions. Thus, although a substantial proportion of the smallest community pharmacies would be spared additional costs, the distribution of Medication Guides by outlets dispensing 96 percent of all prescriptions would be required. Moreover, since patients obtaining unit-of-use prescriptions would receive Medication Guides despite the small pharmacy exemption, it is likely that at least 97 percent of all new prescriptions would be accompanied by patient information.

The third condition is that exempted outlets make available a compilation of Medication Guides for reading in the dispensing or counseling area.

FDA calculates that this small pharmacy exemption would reduce the compliance costs of these proposed regulations to retail pharmacies by 7 percent, while having virtually no effect on manufacturers' costs. This would reduce the expected annual incremental regulatory cost of compliance to $56.3 million. Figure 4 displays these estimates for various exemption options for the retail pharmacy sector.

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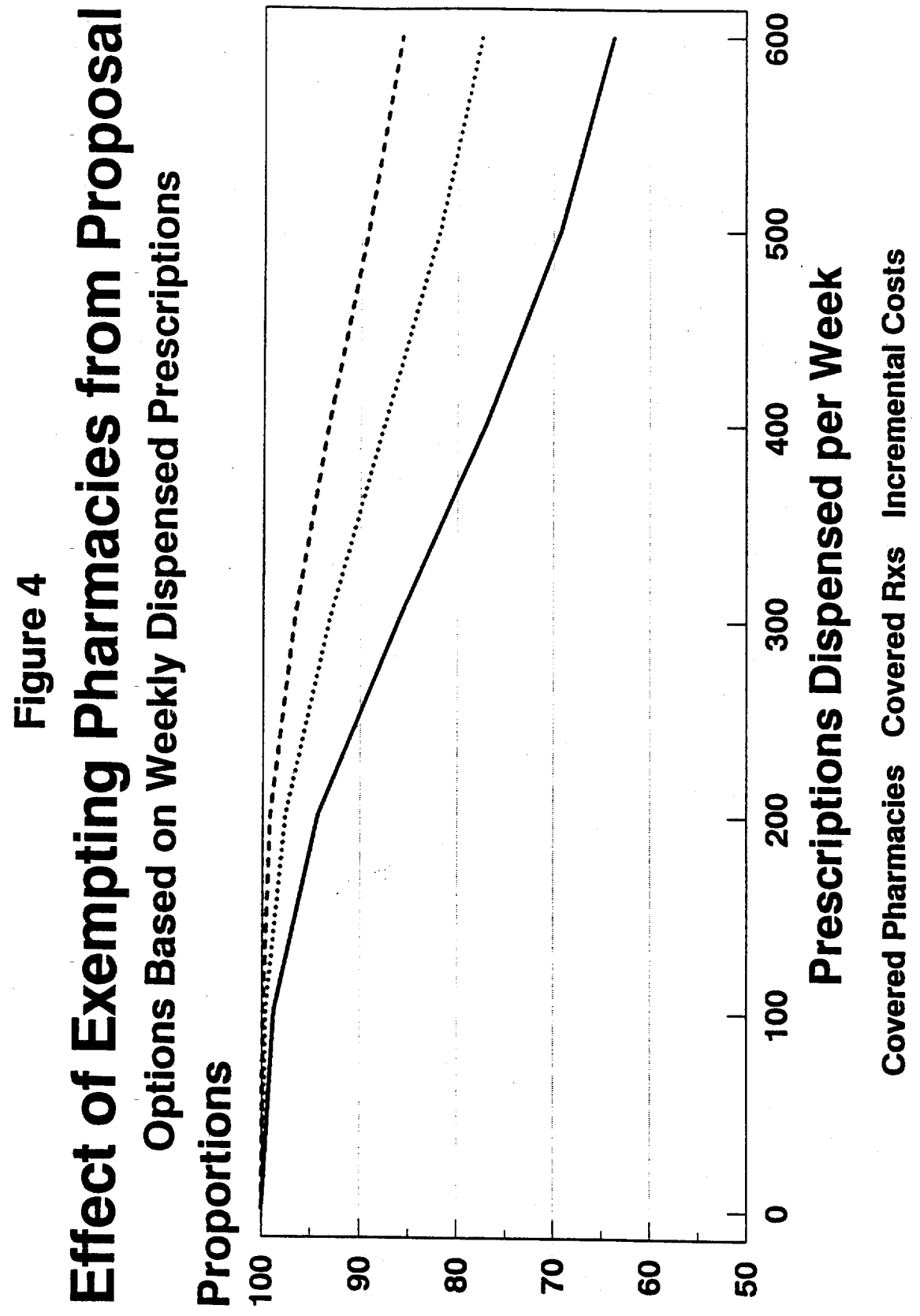

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E. Regulatory Options

Section VII. of this document discussed the advantages and disadvantages of several alternatives to the proposed regulations. The current section presents rough estimates of their potential costs.

Option A, *Continuation of the Status Quo,* would continue current practice. Under this option, FDA would continue to request patient information on an ad hoc basis for specific drug products. Some pharmacies would continue to purchase private product information systems from a variety of vendors for patient distribution, but they would continue to do so voluntarily. Thus, this option would impose no new incremental costs.

Option B, *No Prior FDA Review,* would require that patient information be dispensed with all drug products, but such information would not be approved by the agency prior to distribution. One form of this option reflects the proposed voluntary approach. Over time, compliance costs would approach those estimated for the proposed regulations.

Option C–1, *FDA-Approved Patient Information Available with New Prescriptions and Upon Request,* would require that a Medication Guide be provided with new prescriptions and upon request for refills. This is the proposed regulatory option only if voluntary information efforts are unsuccessful. As derived above, the annual incremental costs to the affected sectors are estimated to reach $56.3 million by the 10th year after implementation, assuming a small business exemption.

Option C–2, *FDA-Approved Patient Information Available with All Prescriptions,* would require that a Medication Guide be provided with both new and refill prescriptions. Although the cost per Medication Guide dispensed decreases slightly because fixed costs are distributed over more guides, the estimated annual incremental costs of compliance for this option are over 40 percent higher than if Medication Guides were only required for new prescriptions and on request for refills. The estimated annual incremental cost of this option is over $80 million.

Option D–1, *Unit-of-Use Packaging,* would require that all prescription drugs, together with Medication Guides, be dispensed in unit-of-use packaging. FDA does not have sufficient information to develop full cost estimates for this option, but believes the requirement would impose additional costs for both new packaging and increased storage space, while reducing product preparation costs. The following projections illustrate the potential magnitude for several of these categories.

The cost to manufacturers of developing and printing the Medication Guides to be enclosed in each drug package would reach about $50 million annually. In addition, the PMA estimated in 1979 that it would cost manufacturers between $25-$29 million to move to unit-of-use packaging. Updating that estimate to current dollars results in approximately $55 million. Moreover, there are about 67 percent more prescription products available today than in 1979, which would boost this estimate further.

Retail pharmacies and wholesalers would need to devote more storage space to unit-of-use drugs. Estimates from the United Kingdom suggest that this type of packaging may increase storage requirements by 40 percent (Ref. 73). A typical pharmacy uses about 500 square feet of floor space. If the 40 percent increment is representative, an annual rental fee of $7.50 per square foot would cost each pharmacy about $1,500. The total annual cost for retail storage would equal $107 million. FDA assumes that wholesalers would experience additional storage costs.

The reduced time for pharmacists to dispense unit-of-use products would offset some of these cost increases. Kaiser Permanente, for example, has estimated that unit-of-use packaging generates time and supply savings of between $0.50 to $1.00 per prescription, although they note that increased packaging costs offset about half of these savings. Other enterprises report lower savings (Ref. 73). FDA recognizes that strict requirements for unit-of-use packaging would have important consequences on these sectors and solicits additional public comment to allow the agency to understand better the associated costs and savings.

Option D–2, *Reference Book at Dispensing Site,* would require only that a book of Medication Guides be made available at the dispensing site. Under this option, manufacturers would continue to bear the same development costs, but the burden on retail pharmacies would be minimal. Even if the insertion of each new or revised Medication Guide into looseleaf binders took only 30 seconds, 200 to 300 annual revisions would entail annual incremental costs to pharmacies of over $2.2 million.

Option D–3, *Interactive Computer Technology,* would permit pharmacies to provide computer access to consumers in lieu of being handed a written Medication Guide. For example, consumers could be directed to a computer kiosk to retrieve automated information. If most consumers opted to print Medication Guides for new prescriptions, the annualized cost of this alternative per pharmacy might average about $100 for computer and printer equipment, $300 for software updates, and $400 for computer supplies. Further, the rental value of a 3 x 3 square foot cubicle in each pharmacy could add another $70 per year (or over $900 if displaced sales are used to value space). These assumptions imply a total annual incremental cost of about $38 million (about $70 million if displaced sales are used to value space).

Option D–4, *Distribution of Books to Consumers,* requires sending or distributing Medication Guide books to each household. The complete book would eventually include several thousand pages and is assumed to cost $5.00 to print. Consequently, if 50 percent of the nation's 95 million households received an annually updated book, the cost of printing would amount to $237.5 million. If the books were distributed from pharmacies, there would be additional costs for storage. If they were annually mailed to each consumer's residence, at a per book postal rate of approximately $2.00, this amounts to an additional $190 million.

Finally, FDA considered option D–5, *Telephone Counseling,* which would require manufacturers of prescription drug and biological products to provide patients with a number to access counseling via telephone. While FDA encourages manufacturers to provide this service voluntarily, the agency believes that this form of oral counseling should be considered an adjunct, not a replacement, for written information. One large, mail-order company reports that about 10 percent of its new prescription customers utilize a toll-free number. This percentage may be an upper-bound, however, when applied to retail outlets where pharmacists are available for counseling at the time of purchase. FDA estimates that if 5 to 10 percent of all new prescription purchases resulted in 3-minute telephone conversations, the annual cost of employing pharmacists to answer these calls would reach $82 to $164 million. In addition, the average telephone charges may equal about $0.30 per minute, adding $50 to $100 million in annual costs. Thus, the estimated incremental costs for this option range from $65 to $132 million.

F. Benefits

The primary objective of the proposed regulation is to enhance the nation's public health by allowing patients to make better use of their medications. FDA believes that the distribution of written prescription drug information to patients, when combined with licensed practitioner and/or pharmacist counseling, would accomplish this goal in two ways. First, it would reduce the incidence of therapeutic failures due to poor compliance with drug regimens. Second, it would decrease the number of preventable adverse drug reactions and preventable drug-drug and drug-food reactions. FDA believes that both outcomes are at least partly attainable with adequate patient knowledge. While there are no definitive studies that would allow FDA to develop precise measures of the present and future levels of these key health variables, this section presents the agency's best assessment of the expected values.

There is substantial literature on the extent of patient noncompliance with prescription drugs. Although a large number of national programs have been initiated to improve patient information and education, this research continues to demonstrate that noncompliance with prescription drug regimens remains a public health concern. A 1990 NCPIE report found that about one-third of patients fail to take their prescribed medications (Ref. 3). An overview of patient compliance studies found that rates of compliance for long-term therapy tend to converge to 50 percent (Ref. 4). Other studies examining the literature on compliance rates in discrete patient populations suggest that pediatric nonadherence to therapeutic regimens exceeds 50 percent (Ref. 5), noncompliance rates for unsupervised psychiatric outpatients range from 25 to 50 percent (Refs. 6 and 7), and noncompliance in the elderly ranges from 26 to 59 percent (Ref. 8). Therefore, FDA has concluded that current patient noncompliance rates range from 30 to 50 percent.

This research also provides evidence that patient noncompliance with prescribed drug regimens is directly related to therapeutic failure with serious health consequences, including blindness, cardiac arrest, and death (Refs. 9 and 10).

A 1990 Office of the Inspector General report found that the process of patient education can save time by reducing calls or visits to the licensed practitioner or pharmacist and by reducing the number of hospitalizations resulting from patients' failures to follow prescribed drug regimens (Ref. 17).

The economic burden to consumers and society of these preventable drug-related illnesses include the direct costs of additional or prolonged treatments by physicians or hospitals and the indirect costs of lost work-time, reduced productivity, and wasted expenditures on drugs whose efficacy is canceled or reduced by inappropriate or improper use. However, only a few studies have addressed the economic costs associated with drug noncompliance. More than 125,000 hospitalizations, and 20 million lost work-days (with lost earnings of $1.5 billion in 1984) were attributed to drug noncompliance related to cardiovascular disease (Ref. 15). A 1990 study of 315 elderly patients found that hospitalization costs totaled approximately $293,000 for all drug-related admissions (Ref. 8) (About $224,000 was attributable to adverse drug reactions and $77,300 for drug noncompliance.) A recent report (Ref. 81) by the Task Force for Compliance, a group of 22 major pharmaceutical companies, estimated that the annual economic costs of noncompliance exceed $100 billion. They attribute these costs to added hospital admissions ($25 billion), prescriptions ($8 billion), nursing home admissions ($5 billion), and lost productivity (over $50 billion).

The most comprehensive recent study employed a meta-analysis to measure the extent and direct costs of hospital admissions related to drug therapy noncompliance, using data on 2,942 hospital admissions from seven studies. Only published studies that met a strict definition of noncompliance (overuse, underuse, or erratic use) were included. The analysis found that 5.3 percent of annual hospital admissions, or 1.94 million admissions, were due to drug noncompliance, at a cost of $8.5 billion in 1986. The author noted that these results were similar to a 1974 Task Force on Prescription Drugs that estimated hospital costs of $3 billion in 1976 dollars for all drug-related admissions (Ref. 15).

As noted above, a precise quantitative measure of the benefits that would result from the increased availability of patient information is not possible, but FDA relied on the studies described above to develop an illustrative example of the potential magnitude of expected benefits. For its best estimate, FDA drew on the 1990 meta-analysis (Ref. 15) to assume that about 5 percent of the nation's 35 million annual hospital admissions are due to noncompliance with prescribed drug regimens. The average cost of each drug-related hospital admission is unknown, but the average cost for all inpatient hospital and physician services is estimated at almost $9,000 per admission (based on 1987 National Medical Expenditure Survey data, updated to 1993 by the Medical Care CPI). As shown in Table 5, the costs of these hospital admissions, based on an average 7-day stay, project to about $15.6 billion per year.

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Table 5

Annual Costs of Preventable Drug-Related Illness

	Number (Millions)	Incidence (Percent)	Unit Cost ($)	Total Cost (Mill. $)
NONCOMPLIANCE:				
Hospital Admissions	35	5.0	8,890	15,558
Unnecessary Rxs	60	5.0	20	60
Physician Visits	60	5.0	39	117
Sub-Total Non-Comp				15,735
ADVERSE REACTIONS:				
Hospital Admissions	35	1.4	8,890	4,387
TOTAL ANNUAL COST				20,122

No comparable studies examined the nonhospital-related costs of drug noncompliance. However, as stated above, FDA found that from 30 to 50 percent of all patients do not currently adhere to prescribed drug regimens. Because an estimated 150 million U.S. consumers use at least one prescription drug per year, about 60 million patients (150 million×40 percent) are at increased risk of added illness. FDA used this figure, together with an estimated incidence rate of 5 percent, to derive a conservative estimate of the percentage of the noncomplying population that would incur other direct medical costs, such as additional medications and physician visits. As shown, the total annual costs of noncompliance, including hospital admissions and other direct costs, are estimated to be about $15.7 billion.

In addition, adverse drug reactions continue to be a significant health problem. FDA believes that appropriate information can moderate these incidents by warning patients about necessary precautions and heightening their ability to understand and respond to adverse reactions. A review of the relevant research in this area indicates that the incidence of adverse drug reactions responsible for hospital admissions ranges from 0.3 to 16.8 percent (Refs. 8, 11, 12, 13, and 14). According to extrapolations from a sample of emergency rooms, approximately 5 percent of drug-related admissions were associated with adverse encounters with OTC drug products, and thus would not be affected by this proposal (Ref. 83). In addition, investigators have estimated that between 48 percent (Ref. 74) and 55 percent (Ref. 84) of all hospital admissions related to adverse reactions are preventable. Thus, using 50 percent as an estimate of preventable adverse reactions, the agency expects that approximately 47 percent (95 percent × 50 percent) of all hospital admissions associated with adverse drug reactions are potentially preventable by the distribution of quality patient information. This equals 1.4 percent of all hospital admissions. As shown in Table 5, these assumptions imply that the costs of preventable adverse drug reactions amount to about $4.4 billion per year. Moreover, although the incidence of adverse drug reactions in ambulatory patients has been reported at 20 percent (Ref. 48), FDA is still examining these data and has not derived estimates of the related costs. In sum, FDA finds that a partial tally of the direct medical costs associated with the additional or prolonged illnesses that result from both noncompliance with prescription drugs and preventable adverse drug reactions adds up to about $20.1 billion a year. Note that this estimate does not include the economic costs of lost productivity. As mentioned above, one pharmaceutical industry task force estimated the annual economic cost of noncompliance related to lost productivity as over $50 billion (Ref. 81).

The realized benefits of increased patient information will depend on the ensuing changes in patient behavior. Several studies since 1982 have found increases in compliance as a result of written information alone or in combination with oral counseling. The rate was as high as 79 percent in the case of a comprehensive patient education program that included additional features (Ref. 74), although in most cases there were more modest increases. Of the studies involving only written information, one found a 30 percent increase in compliance (Ref. 48) and another a 50 percent increase among patients taking penicillin, but no significant difference among patients taking nonsteroidal anti-inflammatory drugs (Ref. 47). Other studies using only written materials found no significant changes in compliance (Refs. 44 and 52). Two studies using both oral and written information showed increased compliance, with increases of 12 to 14 percent (Ref. 49) and 23 percent (Ref. 7). In another study, however, there was no significant effect of oral and written information on compliance (Ref. 66). These studies varied by type of patient, medication, and illness (chronic or acute), definition of compliance, length of therapy, and presence of noticeable symptoms. Such factors may explain the wide variation in the reported effects of written information on drug utilization behavior.

The agency does not anticipate that required patient information would avert the majority of the costs associated with drug-related illnesses. Even with current levels of patient information, significant levels of noncompliance still occur. However, the above studies indicate that understandable information has a significant impact on patient compliance and awareness. Although data are not available to present a precise forecast of the resulting health changes, the agency notes that the health costs described above imply that if patient information was to result in even a 10 percent reduction in adverse outcomes, this would result in benefits of $2 billion per year. A 5-percent improvement would produce annual benefits of $1 billion. Even a 1 percent reduction in these health care expenditures would more than offset the costs of these proposed regulations.

The agency notes that while these figures are only illustrative, it believes that the assumptions upon which they are based are conservative and that the projected range of benefits is reasonable. Moreover, this quantitative estimate does not account for the potential avoidance of catastrophic effects, such as avoidable death, permanent disability, or prolonged hospitalization. The costs of these more severe consequences, at even very low incidence rates, would be substantial.

G. Preliminary Conclusion

Given the enormous benefits in cost savings and improved health care of this program, FDA believes that the economic costs of these regulations are justified. The agency expects concerns to be raised during the comment period about the apparent imbalance in bearing the direct burden of the costs of these proposed regulations, especially as borne by drug manufacturers and retail pharmacies should preapproved Medication Guides be required.

The agency acknowledges that manufacturers would have the primary responsibility for providing required labeling for drug and biological products. FDA has recognized this concern in this proposal by requiring manufacturers to provide the means for the dispenser to generate a sufficient number of Medication Guides. However, as a practical matter, there is a strong possibility that the impact of the proposed patient labeling program, if fully implemented in the absence of satisfactory voluntary efforts, would place a greater share of the financial burden on the retail pharmacy sector rather than the manufacturer. The agency is soliciting guidance on how the costs of a required Medication Guide program could be allocated in a fair and reasonable fashion. Accordingly, in addition to the comments on the reasonableness of the estimates described above, the agency seeks comments on: (1) How manufacturers and pharmacies can share the costs of producing and dispensing Medication Guides; for example, by providing materials, computer support, subsidies, or in some other fashion; and (2) the role third-party intermediaries could play in interfacing between manufacturers and pharmacies, and how they could mitigate costs.

XIII. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) and (a)(11) that this action is of a type that does not

individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XIV. Paperwork Reduction Act of 1980

This proposed rule contains information collections which have been submitted for approval to the Office of Management and Budget under the Paperwork Reduction Act of 1980. The title, description, and respondent description of the information collection are shown below, with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Title: Medication Guide for Prescription Drug Products.

Description: The information collection requirements would impose reporting requirements on manufacturers and a recordkeeping requirement on dispensers. However, until at least the year 2000, this burden would only be required for a small subset of products that pose a serious and significant public health concern requiring immediate distribution of FDA-approved patient information. For these products, manufacturers would be required to develop Medication Guides and submit them to FDA for approval; dispensers would be required to document a good faith effort to obtain Medication Guides when their supply is low or depleted.

Description of Respondents: Businesses.

ESTIMATED ANNUAL REPORTING AND RECORDKEEPING BURDEN

21 CFR section	Annual number of responses	Annual frequency	Average burden per response	Annual burden hours
208.26(c)	521	NA	30 min.	261
314.50 (c)(2)(i), (d)(5)(vi)(*b*), and (e)(2)(ii); and 601.2(a)	10	1	320 hrs.	3,200
314.70(b)(3)(ii)	20	1	160 hrs.	3,200
314.94 (a)(8)(i), (a)(8)(ii), (a)(8)(iii), and (a)(8)(iv); and 314.97	10	1	16 hrs.	160
Total				6,821

The agency has submitted a copy of this proposed rule to the Office of Management and Budget (OMB) for its review of these information collections. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to FDA's Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, OMB, Washington, DC 20503.

XV. Federalism

Executive Order 12612, Federalism, is intended to ''restore the division of governmental responsibilities between the national government and the States that was intended by the Framers of the Constitution and to ensure that the principles of federalism established by the Framers guide the Executive departments and agencies in the formulation and implementation of policies.'' Section 3(d)(3) of Executive Order 12612 states that, when national standards are required, agencies must consult appropriate State officials and organizations. Section 4(d) requires agencies that foresee any possible conflict between State laws and federally protected interests to consult, to the extent practicable, appropriate officials and organizations representing the States to avoid such conflict.

FDA is aware that several States have laws or regulations that require pharmacists to counsel patients on the use of prescription drug products. The agency does not believe its proposed rule on Medication Guides conflicts with such laws or regulations because the proposed rule would not affect any oral counseling requirement imposed by State laws or regulations. Nevertheless, the agency will continue to examine State laws for federalism purposes and invites comments from interested persons, particularly with respect to State initiatives to provide information on prescription drug products to patients.

XVI. References

The following information has been placed on display in the Dockets Management Branch (address above) where it may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Green, L. W., P. D. Mullen, and R. B. Friedman, ''An Epidemiological Approach to Targeting Drug Information,'' *Patient Education and Counseling*, 8:255–268, 1986.
2. Morris, L. A., et al., ''A Segmentational Analysis of Prescription Drug Information Seeking,'' *Medical Care*, 25:953–964, 1987.
3. Heyduk, L. J., ''Medication Education: Increasing Patient Compliance,'' *Journal of Psychosocial Nursing*, 29:32–35, 1991.
4. Morris, L. S., and R. M. Schulz, ''Patient Compliance—An Overview,'' *Journal of Clinical Pharmacy and Therapeutics*, 17:283–295, 1992.
5. Bartlett, E. E., ''Effective Approaches to Patient Education for the Busy Pediatrician,'' *Pediatrics*, 74:920–923, 1984.
6. Voris, J., C. Morin, and J. S. Kiel, ''Monitoring Outpatients' Plasma Antidepressant-Drug Concentrations as a Measure of Compliance,'' *American Journal of Hospital Pharmacy*, 40:119–120, 1983.
7. Robinson, G. L., A. D. Gilbertson, and L. Litwack, ''The Effects of a Psychiatric Patient Education to Medication Program on Post-Discharge Compliance,'' *Psychiatric Quarterly*, 58(2):113–118, Summer 1986–1987.
8. Col, N., J. E. Fanale, and P. Kronholm, ''The Role of Medication Noncompliance and Adverse Drug Reactions in Hospitalizations of the Elderly,'' *Archives of Internal Medicine*, 150:841–845, 1990.
9. Office of the Inspector General, Office of Evaluation and Inspections, ''Medication Regimens: Causes of Noncompliance,'' March 1990, citing John Urquhart, ''Drug Delivery Technology and Patient Compliance for New Products;'' Paper presented at The Conference on Advanced Therapeutics: Overcoming End User Barriers. Co-sponsored by the National Pharmaceutical Council and Frost and Sullivan, Baltimore, April 17–18, 1989.
10. Wood, A. J. J., and J. A. Oates, ''Adverse Reactions to Drugs,'' In Petersdorf, R., *et al.*, ''Harrison's Principles of Internal Medicine,'' 12th ed. New York, McGraw-Hill; 373–379, 1991.
11. Lakshmanan, M. C., C. O. Hershey, and D. Breslau, ''Hospital Admissions Caused by Iatrogenic Disease,'' *Archives of Internal Medicine*, 146:1931–1934, 1986.
12. Salem, R. B., T. M. Keane, and J. G. Williams, ''Drug-Related Admissions to a Veterans' Administration Psychiatric Unit,'' *Drug Intelligence and Clinical Pharmacy*, 18:74–76, 1984.
13. Ives, T. I., E. J. Bentz, and R. E. Gwyther, ''Drug-Related Admissions to a Family Medicine Inpatient Service,'' *Archives of Internal Medicine*, 147:1117–1120, 1987.
14. Schneider, J. K., L. C. Mion, and J. D. Frengley, ''Adverse Drug Reactions in an

Elderly Outpatient Population,'' *American Journal of Hospital Pharmacy*, 49:90–96, 1992.
15. Sullivan, S. D., D. H. Kreling, and T. K. Hazlet, ''Noncompliance with Medication Regimens and Subsequent Hospitalizations: A Literature Analysis and Cost of Hospitalization Estimate,'' *Journal of Research in Pharmaceutical Economics*, 2(2):19–23, 1990.
16. Murphy, J. A., et al., ''Amiodarone: A Postmarketing Evaluation of Monitoring for Drug Induced Toxicity,'' *DICP—Drug Intelligence and Clinical Pharmacy*, 24:1001–1005, 1990.
17. Office of the Inspector General, Office of Evaluation and Inspections, ''Medication Regimens: Causes of Noncompliance,'' March 1990.
18. National Council on Patient Information and Education, ''Directory of Prescription Drug Information and Education Programs and Resources,'' Bullman, W. R., and F. Rowland (ed.), 1985.
19. Morris, L. A., E. R. Tabak, and N. J. Olins, ''A Segmentation Analysis of Prescription Drug Information-Seeking Motives Among the Elderly,'' *Journal of Public Policy and Marketing*, 11(2):115–125, 1992.
20. Morris, L. A., and M. D. Tyson, ''There's More Than One Way to Go Direct to the Consumer,'' *Perspectives*, 9:5–12, 1985.
21. ''Direct to Consumer Advertising of Prescription Drugs; Withdrawal of Moratorium,'' **Federal Register**, 50 FR 36677–36678, September 9, 1985.
22. Morris, L. A., et al., ''Patient Receipt of Prescription Drug Information,'' National Technical Information Service, No. PB84–100031, Springfield, VA.
23. Morris, L. A., et al., ''A National Survey of Prescription Drug Information Provided to Patients,'' National Technical Information Service, No. PB86–186947/XAB, 1986, Springfield, VA.
24. Morris, L. A., et al., ''Counseling Patients About Prescribed Medication: Ten Year Trends,'' Food and Drug Administration, Rockville, MD, 1993.
25. ''Public Attitudes Toward Prescription Drug Information: A Nationwide Study Conducted for CBS Inc.,'' Response Analysis Corp., Princeton, NJ, 1984.
26. Abram, M. B., ''Making Health Care Decisions: The Ethical and Legal Implications of Informed Consent in the Patient-Practitioner Relationship,'' President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, October 1982.
27. Wiederholt, J. B., B. R. Clarridge, and B. L. Svarstad, ''Verbal Consultation Regarding Prescription Drugs: Findings from a Statewide Survey,'' *Medical Care*, 30:159–173, 1992.
28. Ascione, F. J., et al., ''A Survey of Patient Education Activities of Community Pharmacists,'' *Patient Education and Counseling*, 7:359–366, 1985.
29. McMahon, T., C. M. Clark, and G. R. Bailie, ''Who Provides Patients with Drug Information?'' *British Medical Journal*, 294:355–356, 1987.
30. Katz, J. N., et al., ''Informed Consent and the Prescription of Nonsteroidal Antiinflammatory Drugs,'' *Arthritis and Rheumatism*, 35:1257–1263, 1992.
31. Murphy, J. A. M., et al., ''Amiodarone: A Postmarketing Evaluation of Monitoring for Drug-Induced Toxicity,'' *DICP, The Annals of Pharmacotherapy*, 24:1001–1005, 1990.
32. McClellan, W., ''The Physician and Patient Education: A Review,'' *Patient Education and Counseling*, 8:151–163, 1986.
33. Gardner, M. E., et al., ''A Study of Patients' Perceived Importance of Medication Information Provided by Physicians in a Health Maintenance Organization,'' *Drug Intelligence and Clinical Pharmacy*, 22:596–598, 1988.
34. Nightingale, S. L., ''Do Physicians Tell Patients Enough About Prescription Drugs? Do Patients Think So?'' *Postgraduate Medicine*, 74:170–175, 1983.
35. Graham, A. V., T. V. Parran, and C. R. Jaen, ''Physician Failure to Record Alcohol Use History When Prescribing Benzodiazepines,'' *Journal of Substance Abuse*, 4:179–185, 1992.
36. Ley, P., ''Communicating with Patients: Improving Communication, Satisfaction and Compliance,'' D. Marcer, ed., Croom Helm, New York, 1988.
37. Debrovner, D., ''What Consumers Think About You,'' *American Druggist*, 24–31, 1993.
38. Weinman, J., ''Providing Written Information for Patients: Psychological Considerations,'' *Journal of the Royal Society of Medicine*, 83:303–305, 1990.
39. Williams-Deane, M., and L. S. Potter, ''Current Oral Contraceptive Use Instructions: An Analysis of Patient Package Inserts,'' *Family Planning Perspectives*, 24:111–115, 1992.
40. Casey, F. G., D. M. Fluitt, and A. L. Wiatt, ''The Patient's Understanding of the Oral Contraceptive Patient Package Insert,'' *Military Medicine*, 148:276–278, 1983.
41. O'Connell, M. B., and J. F. Johnson, ''Evaluation of Medication Knowledge in Elderly Patients,'' *The Annals of Pharmacotherapy*, 26:919–921, 1992.
42. Gibbs, S., W. E. Waters, and C. F. George, ''Communicating Information to Patients About Medicine,'' *Journal of the Royal Society of Medicine*, 83:292–296, 1990.
43. Harvey, J. L., and R. J. Plumridge, ''Comparative Attitudes to Verbal and Written Medication Information Among Hospital Outpatients,'' *DICP, The Annals of Pharmacotherapy*, 25:925–928, 1991.
44. Gibbs, S., W. E. Waters, and C. F. George, ''The Benefits of Prescription Information Leaflets (1),'' *British Journal of Clinical Pharmacology*, 27:723–739, 1989.
45. Van Haecht, C. H. M., R. Vander Stichele, and M. G. Bogaert, ''Package Inserts for Antihypertensive Drugs: Use by the Patient and Impact on Adverse Drug Reactions,'' *European Journal of Clinical Pharmacology*, 39:551–554, 1990.
46. Sandler, D. A., et al., ''Is an Information Booklet for Patients Leaving Hospital Helpful and Useful?'' *British Medical Journal*, 298:870–874, 1989.
47. George, C. F., W. E. Waters, and J. A. Nicholas, ''Prescription Information Leaflets: A Pilot Study in General Practice,'' *British Medical Journal*, 287:1193–1196, 1983.
48. Dodds, L. J., ''Effects of Information Leaflets on Compliance with Antibiotic Therapy,'' *The Pharmaceutical Journal*, 11:48–51, 1986.
49. Myers, E. D., and E. J. Calvert, ''Information, Compliance and Side-Effects: A Study of Patients on Antidepressant Medication,'' *British Journal of Clinical Pharmacology*, 17:21–25, 1984.
50. Drury, V. W. M., ''Patient Information Leaflets,'' *British Medical Journal*, 288:427–428, 1984.
51. Hays, R. D., and M. R. DiMatteo, ''Key Issues and Suggestions for Patient Compliance Assessment: Sources of Information, Focus of Measures, and Nature of Response Options,'' *The Journal of Compliance in Health Care*, 2:37–53, 1987.
52. Gibbs, S., W. E. Waters, and C. F. George, ''The Benefits of Prescription Information Leaflets (2),'' *British Journal of Clinical Pharmacology*, 28:345–351, 1989.
53. Gibbs, S. ''Prescription Information Leaflets for Patients,'' *European Respiratory Journal*, 5:140–143, 1992.
54. Proos, M., et al., ''A Study of the Effects of Self-Medication on Patients' Knowledge of and Compliance with Their Medication Regimen,'' *Journal of Nursing Care Quality*, Special Report: 18–26, 1992.
55. Schwartz-Lookinland, S., L. C. McKeever, and M. Saputo, ''Compliance with Antibiotic Regimens in Hispanic Mothers,'' *Patient Education and Counseling*, 13:171–182 1989.
56. Haynes, R. B., E. Wang, and M. D. M. Gomes, ''A Critical Review of Interventions to Improve Compliance with Prescribed Medications,'' *Patient Education and Counseling*, 10:155–166 1987.
57. Prince, B. S., et al., ''Drug-Related Emergency Department Visits and Hospital Admissions,'' *American Journal of Hospital Pharmacy*, 49:1696–1700, 1992.
58. Wiederholt, J. B., and J. A. Kotzan, ''Effectiveness of the FDA-Designed Patient Package Insert for Benzodiazepines,'' *American Journal of Hospital Pharmacy*, 40:828–834, 1983.
59. Morrow, N. C., ''Printed Information for Patients Receiving PUVA Therapy,'' *Journal of Clinical and Hospital Pharmacy*, 9:333–340, 1984.
60. Hawkey, G. M., and C. J. Hawkey, ''Effect of Information Leaflets on Knowledge in Patients with Gastrointestinal Diseases,'' *Gut*, 30:1641–1646, 1989.
61. Dolinsky, D., et al., ''Application of Psychological Principles to the Design of Written Patient Information,'' *American Journal of Hospital Pharmacy*, 40:266–271, 1983.
62. Morris, L. A., and D. E. Kanouse, ''Informing Patients About Drug Side Effects,'' *Journal of Behavioral Medicine*, 5:363–373, 1982.
63. Fisher, S., and S. G. Bryant, ''Postmarketing Surveillance: Accuracy of Patient Drug Attribution Judgments,'' *Clinical Pharmacological Therapy*, 48:102–107, 1990.
64. Quaid, K. A., et al., ''Informed Consent for a Prescription Drug: Impact of Disclosed Information on Patient

Understanding and Medical Outcomes,'' *Patient Education and Counseling*, 15(3):249–259, 1990.
65. Howland, S., M. G. Baker, and T. Poe, ''Does Patient Education Cause Side Effects? A Controlled Trial,'' *The Journal of Family Practice*, 31:62–64, 1990.
66. Brown, C. S., R. G. Wright, and D. B. Christensen, ''Association Between Type of Medication Instruction and Patients' Knowledge, Side Effects, and Compliance,'' *Hospital and Community Psychiatry*, 38(1):55-60, 1987.
67. Regner, M. J., F. Hermann, and L. D. Ried, ''Effectiveness of a Printed Leaflet for Enabling Patients to Use Digoxin Side-Effect Information,'' *Drug Intelligence and Clinical Pharmacy*, 21:200–204, 1987.
68. Mullen, P. D., and L. W. Green, ''Measuring Patient Drug Information Transfer: An Assessment of the Literature,'' Pharmaceutical Manufacturers Association, Washington, DC, 1983.
69. Kanouse, D. E., *et al.*, ''Informing Patients About Drugs: Summary Report on Alternative Designs for Prescription Drug Leaflets,'' Rand Corp., Santa Monica, CA, 1981.
70. 42 U.S.C. 1396r–8(g)(2)(A)(ii)(I).
71. Council Directive 92/27/EEC, 1992 O.J. (L 113) 8–12.
72. Kirsch, I. S., *et al.*, ''Adult Literacy in America,'' Office of Educational Research and Improvement, U.S. Department of Education, September 1993.
73. Proceedings of Conference on Unit-of-Use Packaging Contemporary Issues, December 13 through 15, 1992.
74. Sclar, D., *et al.*, ''Effect of Health Education in Promoting Prescription Refill Compliance Among Patients with Hypertension,'' *Clinical Therapeutics*, 13:489–495, 1991.
75. National Association of Chain Drug Stores, ''Prescription Drug Marketplace Simulation Model,'' 1992.
76. Banahan and Garner, ''Using Pharmacy Computer Systems for Better Patient Care,'' *Drug Topics*, p. 82, January 10, 1994.
77. ''Home Health, Mail Order Lead Pharmacy Gainers,'' *Drug Topics*, pp. 15–16, September 6, 1993.
78. *1992 Lilly Digest*, Eli and Co., 1992.
79. ''An Assessment of Chain Pharmacies' Costs of Dispensing a Third Party Prescription,'' prepared by the Pharmaceutical Economics Research Center, Purdue University for the National Association of Chain Drug Stores, May 1990.
80. ''Annual Report of Retail Pharmacy,'' *Drug Store News*, April 20, 1992, supplement.
81. Task Force for Compliance, ''Noncompliance with Medications: An Economic Tragedy with Important Implications for Health Care Reform,'' Baltimore, MD, November 1993.
82. Tabak, E. R., ''Encouraging Patient Question-Asking: A Clinical Trial,'' *Patient Education and Counseling*, 12:37–49, 1988.
83. The Drug Abuse Warning Network, Annual Emergency Room Data 1992, U.S. Department of Health and Human Services; Substance Abuse and Mental Health Services Administration, Series I, Number 12–A, p. 44.
84. Burnam, J. F., ''Preventability of Adverse Drug Reactions,'' *Annals of Internal Medicine*, 85:80–81, 1976.
85. Backinger, C. L., and P. A. Kingsley, ''Write It Right: Recommendations for Developing User Instructions for Medical Devices Used in Home Health Care,'' Department of Health and Human Services, Publication FDA 93–4258, 1993.
86. Doak, C. C., L. G. Doak, and J. H. Root, ''Teaching Patients With Low Literacy Skills,'' Philadelphia, J. B. Lippincott Co., 1985.
87. Felker, D. B., F. Pickering, V. R. Charrow, V. M. Holland, and J. C. Redish, Guidelines for Document Designers, Washington, DC, American Institutes for Research, 1981.
88. Mettger, W. and J. Mara, ''Clear and Simple: Developing Print Materials for Low-literacy Readers,'' Bethesda, MD, National Cancer Institute, 1992.
89. Morris, L. A., M. Mazis, and E. Gordon, ''A Survey of the Effects of Oral Contraceptive Patient Information,'' *Journal of the American Medical Association*, 238(23):2504–2508, 1977.
90. Morris, L. A., A. Myers, P. Gibbs, and C. Lao, ''Estrogen PPIs: An FDA Survey,'' *American Pharmacy*, NS20(6):22–26, 1980.
91. Lamb, G. C., S. S. Green, and J. Heron, ''Can Physicians Warn Patients of Potential Side Effects Without Fear of Causing Those Side Effects?,'' *Archives of Internal Medicine*, 154:2753–2756, 1994.
92. Kessler, D. A., ''Communicating With Patients About Their Medications,'' *New England Journal of Medicine*, 325:1650–1652, 1991.
93. Scheman, C. R., ''Patient Information and Education About Drugs: The FDA Perspective,'' *Drug Information Journal*, 27:1133–1136, 1993.
94. Morris, L. A., D. Brinberg, R. Klimberg, L. Millstein, and C. Rivera, ''Consumer Attitudes About Advertisements for Medicinal Drugs,'' *Social Science and Medicine*, 22:629–638, 1986.
95. National Association of Boards of Pharmacy, ''Consumer Patient Counseling Survey,'' 1994.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 208

Drugs, Patient labeling, Reporting and recordkeeping requirements.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedures, Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that Chapter I of Title 21 of the Code of Federal Regulations be amended to read as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 510, 512, 530–542, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg-360ss, 371, 374, 379e); secs. 215, 301, 351, 361 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 264).

2. Section 201.57 is amended by revising paragraph (f)(2) to read as follows:

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

* * * * *

(f) * * *

(2) Information for patients: This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug, e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects. Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the ''Precautions'' section of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling. The print size requirements for patient information or the Medication Guide set forth in § 208.22 of this chapter, however, do not apply to patient information or the Medication Guide that is reprinted in the professional labeling.

* * * * *

3. New part 208 is added to read as follows:

PART 208—MEDICATION GUIDE FOR PRESCRIPTION DRUG PRODUCTS

Subpart A—General Provisions

Sec.

Subpart B—General Requirements for a Medication Guide

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 510, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360, 371,

374); Sec. 351 of the Public Health Service Act (42 U.S.C. 262).

Subpart A—General Provisions

§ 208.1 Scope and implementation.

(a) This part sets forth requirements for patient labeling for human prescription drug products, including biological products. It applies only to those human prescription drug products administered primarily on an outpatient basis without direct supervision by a health professional. This part shall apply to new prescriptions and upon request by the patient for refill prescriptions. This part does not apply to prescription drug products administered in an institutional setting (such as hospitals, nursing homes, or other health care facilities), or in emergency situations.

(b) Except as provided in paragraph (d) of this section, the provisions of this part are deferred until a determination is made by FDA that either of the following performance standards has not been met:

(1) by (*insert date 5 years from the effective date of the final rule*), 75 percent of patients receiving new prescription drugs or biologics that are covered under these provisions receive useful patient information as described in paragraph (c) of this section, or

(2) by (*insert date 11 years from the effective date of the final rule*), 95 percent of the patients receiving new prescription drugs or biologics that are covered under these provisions receive useful patient information as described in paragraph (c) of this section.

(c) Determination of useful patient information will be based on scientific accuracy, consistency with the format in § 208.22, nonpromotional tone and content, specificity, comprehensiveness, understandable language, and legibility.

(d) This part shall apply without deferral to human prescription drug products and biological products that FDA determines pose a serious and significant public health concern requiring immediate distribution of FDA-approved patient information.

§ 208.3 Definitions.

For purposes of this part, the following definitions shall apply:

(a) *Authorized dispenser* means an individual licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to provide drug products on prescription in the course of professional practice.

(b) *Dispense to patients* means the act of delivering a prescription drug product to a patient or an agent of the patient either:

(1) By a licensed practitioner or an agent of a licensed practitioner, either directly or indirectly, for self-administration by the patient, or the patient's agent, or outside the licensed practitioner's direct supervision; or

(2) By an authorized dispenser or an agent of an authorized dispenser under a lawful prescription of a licensed practitioner.

(c) *Distribute* means the act of delivering, other than by dispensing, a drug product to any person.

(d) *Distributor* means a person who distributes a drug product.

(e) *Licensed practitioner* means an individual licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to prescribe drug products in the course of professional practice.

(f) *Manufacturer* means the manufacturer as described in §§ 201.1 and 600.3(t) of this chapter.

(g) *Patient* means any individual, with respect to whom a drug product is intended to be, or has been, used.

Subpart B—General Requirements for a Medication Guide

§ 208.20 Content of a Medication Guide.

(a) A Medication Guide shall meet all of the following conditions:

(1) The Medication Guide shall be written in English, in nontechnical language, and shall not be promotional in tone or content.

(2) The Medication Guide shall be based on, and shall not conflict with, the approved professional labeling for the drug product under § 201.57 of this chapter.

(b) A Medication Guide shall contain the following:

(1) The brand name (e.g., the trademark or proprietary name), if any, and established name. Those products not having an established name shall be designated by their active ingredients. The Medication Guide shall include the phonetic spelling of either the brand name or the established name, whichever is used throughout the Medication Guide.

(2) A summary section containing the drug product's approved indications, critical aspects of proper use, significant warnings, precautions, and contraindications, serious adverse reactions, and potential safety hazards.

(3) A section that identifies a drug product's indications for use. The Medication Guide may not identify an indication unless the indication is identified in the indications and usage section of the professional labeling for the product required under § 201.57 of this chapter.

(4) Information on circumstances under which the drug product should not be used for its labeled indication (its contraindications). The Medication Guide shall contain directions regarding what to do if any of the contraindications apply to a patient, such as contacting the licensed practitioner or discontinuing use of the drug product.

(5) A statement or statements of precautions the patient should take to ensure proper use of the drug, including:

(i) A statement that identifies activities (such as driving or sunbathing), and drugs, foods, or other substances (such as tobacco or alcohol) that the patient should avoid;

(ii) A statement of the risks to the mother and fetus from the use of the drug during pregnancy;

(iii) A statement of the risks of the drug product to a nursing infant;

(iv) A statement of pediatric indications, if any. If the drug product has specific hazards associated with its use in pediatric patients, a statement of the risks;

(v) A statement of geriatric indications, if any. If the drug product has specific hazards associated with its use in geriatric patients, a statement of the risks; and

(vi) A statement of special precautions, if any, that apply to the safe and effective use of the drug product in other identifiable patient populations.

(6)(i) A statement of the possible adverse reactions from the use of the drug product which are serious or occur frequently.

(ii) A statement of the risks, if any, to the patient of developing a tolerance to, or dependence on, the drug product.

(7) Information on the proper use of the drug product, including:

(i) A statement stressing the importance of adhering to the dosing instructions.

(ii) A statement describing any special instructions on how to administer the drug product.

(iii) A statement of what the patient should do in case of overdose of the drug product.

(iv) A statement of what the patient should do if the patient misses taking a scheduled dose of the drug product.

(8) General information about the safe and effective use of prescription drug products, including:

(i) The verbatim statement that ''Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide'' followed by a statement that the patient should ask the health professional about any concerns,

and a reference to the availability of professional labeling;

(ii) A statement that the drug product not be used for other conditions or given to other persons;

(iii) The name and place of business of the manufacturer, packer, or distributor, as required for the label of the drug product under § 201.1 of this chapter, or the name and place of business of the dispenser of the drug product or for biological products, the name, address, and license number of the manufacturer; and

(iv) The date, identified as such, of the most recent revision of the Medication Guide placed immediately after the last section.

§ 208.22 Format for a Medication Guide.

A Medication Guide shall be printed in accordance with the following specifications:

(a) The letter height or type size shall be no smaller than 10 points (1 point = 0.0138 inches) for all sections of the Medication Guide, except the manufacturer's name and address and the revision date.

(b) The Medication Guide shall be legible and clearly presented. Where appropriate, the Medication Guide shall also use boxes, bold or underlined print, or other highlighting techniques to emphasize specific portions of the text.

(c) The words ''Medication Guide'' shall appear prominently at the top of the first page of a Medication Guide. The verbatim statement ''This Medication Guide has been approved by the U.S. Food and Drug Administration'' shall appear at the bottom of a Medication Guide.

(d) The brand and established name shall be immediately below the words ''Medication Guide.'' The established name shall be no less than one-half the height of the brand name.

(e) The Medication Guide shall use the following headings:

(1) ''What is the most important information I should know about (name of drug)?''

(2) ''What is (name of drug)?''

(3) ''Who should not take (name of drug)?''

(4) ''How should I take (name of drug)?''

(5) ''What should I avoid while taking (name of drug)?''

(6) ''What are the possible side effects of (name of drug)?''

§ 208.24 Distributing and dispensing a Medication Guide.

(a) For a large volume container of finished dosage form:

(1) Each manufacturer shall provide to each distributor to which it ships a large volume container of finished dosage form either:

(i) The Medication Guide in sufficient numbers; or

(ii) The means to produce the Medication Guide in sufficient numbers to permit the distributor to comply with paragraph (b) of this section.

(2) The label of each large volume container of finished dosage form shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed.

(b) Each manufacturer or distributor shall provide to each authorized dispenser to which it ships the drug product either:

(1) The Medication Guide in sufficient numbers; or

(2) The means to produce the Medication Guide in sufficient numbers to permit the authorized dispenser to provide the Medication Guide to each patient receiving a new prescription for a drug product or requesting a Medication Guide.

(c) For a drug product in a unit-of-use container, the manufacturer and distributor shall provide a Medication Guide with each package of the drug product that the manufacturer or distributor intends to be dispensed to patients.

(d) The requirements of this section can be met by the manufacturer or distributor or by any other person acting on behalf of the manufacturer or distributor. Nothing in this section prohibits a manufacturer or distributor from meeting the requirements with a Medication Guide printed by the distributor or authorized dispenser.

(e) Each authorized dispenser of a prescription drug product subject to this part shall, when the product is dispensed (to a patient or to a patient's agent), for new prescriptions and upon request by the patient for refill prescriptions, provide a Medication Guide directly to each patient (or to the patient's agent), unless an exemption applies under § 208.26.

(f) An authorized dispenser is not subject to section 510 of the Federal Food, Drug, and Cosmetic Act, which requires the registration of producers of drugs and the listing of drugs in commercial distribution solely because of an act performed by the authorized dispenser under part 208.

§ 208.26 Exemptions and deferrals.

(a) The Food and Drug Administration (FDA) on its own initiative or in response to a written request from an applicant, may exempt or defer any or all Medication Guide requirements on the basis that the requirement is inapplicable, unnecessary, or contrary to the patient's best interests. Requests from applicants should be submitted to the director of the FDA division responsible for reviewing the marketing application for the drug product, or for a biological product, to the application division in the office with product responsibility.

(b) If the licensed practitioner who prescribes a drug product, or the authorized dispenser who dispenses a drug product, determines that it is not in the patient's best interest to receive a Medication Guide because of significant concerns about the effect of a Medication Guide, the licensed practitioner may direct that the Medication Guide not be provided to the patient, or the authorized dispenser may withhold the Medication Guide. However, the authorized dispenser of a prescription drug product shall provide a Medication Guide to any patient who requests it when the drug product is dispensed regardless of any such direction by the licensed practitioner or the authorized dispenser. This exemption from providing a Medication Guide does not apply if FDA determines that a Medication Guide for a particular product should be provided to all patients under all circumstances.

(c) A Medication Guide is not required to be dispensed to patients in emergency situations or where the manufacturer, distributor, or authorized dispenser, after documenting a good faith effort to obtain a Medication Guide for the patient, does not have a Medication Guide available for the patient.

(d)(1) An authorized dispenser, as defined in § 208.3(a), shall be exempt from the dispensing requirements of § 208.24(e) when the following conditions are met:

(i) The authorized dispenser dispensed, in the previous calendar year, no more than an average of 300 outpatient prescription drug products per week; and

(ii) The authorized dispenser, or its business entity, has gross annual sales of no more than $5.0 million; and

(iii) The authorized dispenser makes available to patients a compilation of current Medication Guides for reading in the dispensing or counseling area.

(2) This exemption does not apply to a drug dispensed in a unit-of-use container or a drug which the agency determines must be dispensed with a Medication Guide.

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

4. The authority citation for 21 CFR part 314 is revised to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

5. Section 314.50 is amended by revising the first and third sentences of the introductory text, paragraph (c)(2)(i), the first sentence of paragraph (d)(5)(vi)(*b*), paragraph (e)(2)(ii), and the fourth sentence in paragraph (k)(1) to read as follows:

§ 314.50 Content and format of an application.

Applications and supplements to approved applications are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. * * * An application for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling, including, if applicable, any Medication Guide required under part 208 of this chapter. * * *

* * * * *

(c) * * *

(2) * * *

(i) The proposed text of the labeling, including, if applicable, any Medication Guide required under part 208 of this chapter, for the drug, with annotations to the information in the summary and technical sections of the application that support the inclusion of each statement in the labeling, and, if the application is for a prescription drug, statements describing the reasons for omitting a section or subsection of the labeling format in § 201.57 of this chapter.

* * * * *

(d) * * *

(5) * * *

(vi) * * *

(*b*) The applicant shall, under section 505(i) of the act, update periodically its pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and, if appropriate, any Medication Guide required under part 208 of this chapter. * * *

* * * * *

(e) * * *

(2) * * *

(ii) Copies of the label and all labeling for the drug product (including, if applicable, any Medication Guide required under part 208 of this chapter) for the drug product (4 copies of draft labeling or 12 copies of final printed labeling).

* * * * *

(k) * * *

(1) * * * Information relating to samples and labeling (including, if applicable, any Medication Guide required under part 208 of this chapter), is required to be submitted in hard copy. * * *

* * * * *

6. Section 314.70 is amended by revising paragraph (b)(3) to read as follows:

§ 314.70 Supplements and other changes to an approved application.

* * * * *

(b) * * *

(3) *Labeling.* (i) Any change in labeling, except one described in paragraphs (c)(2) or (d) of this section.

(ii) If applicable, any change to a Medication Guide required under part 208 of this chapter.

* * * * *

7. Section 314.94 is amended by revising paragraph (a)(8) to read as follows:

§ 314.94 Content and format of an abbreviated application.

* * * * *

(a) * * *

(8) *Labeling*—(i) *Listed drug labeling.* A copy of the currently approved labeling (including, if applicable, any Medication Guide required under part 208 of this chapter) for the listed drug referred to in the abbreviated new drug application, if the abbreviated new drug application relies on a reference listed drug.

(ii) *Copies of proposed labeling.* Copies of the label and all labeling for the drug product (including, if applicable, any Medication Guide required under part 208 of this chapter) for the drug product (4 copies of draft labeling or 12 copies of final printed labeling).

(iii) *Statement on proposed labeling.* A statement that the applicant's proposed labeling (including, if applicable, any Medication Guide required under part 208 of this chapter) is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section.

(iv) *Comparison of approved and proposed labeling.* A side-by-side comparison of the applicant's proposed labeling (including, if applicable, any Medication Guide required under part 208 of this chapter) with the approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

* * * * *

PART 601—LICENSING

8. The authority citation for 21 CFR part 601 is revised to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 513–516, 518–520, 701, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381); secs. 215, 301, 351, 352 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461).

9. Section 601.2 is amended in paragraph (a) by revising the first sentence to read as follows:

§ 601.2 Applications for establishment and product licenses; procedures for filing.

(a) *General.* To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Center for Biologics Evaluation and Research, on forms prescribed for such purposes, and in the case of an application for a product license, shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the

reason for the noncompliance; statements regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter or was not subject to such requirements in accordance with § 56.104 or § 56.105 of this chapter, and was conducted in compliance with requirements for informed consent set forth in part 50 of this chapter; a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried, or brought for sale, barter, or exchange; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of the labels, enclosures, containers, and, if applicable, any Medication Guide required under part 208 of this chapter proposed to be used for the product. * * *

* * * * *

Dated: July 17, 1995.

David A. Kessler,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

Note: The following appendixes will not appear in the Code of Federal Regulations.

BILLING CODE 4160–01–P

APPENDIX A—A "shell" of the proposed uniform format

BILLING CODE 4160–01–C

APPENDIX B—Several sample Medication Guides using the proposed uniform format

Appendix B

Medication Guide

Questions and Answers About

Ceclor

(generic name = cefaclor for oral suspension)

What is the most important information I should know about Ceclor?

Ceclor (pronounced SEE-klor) is used to treat infections caused by certain bacteria. You should not take Ceclor if you are allergic to penicillin or other similar antibiotics. Allergic reactions to Ceclor, as with other drugs, can be fatal. If you experience difficulty breathing, swelling of the throat, rash, or severe diarrhea or abdominal pain, call your doctor immediately or seek medical help.

Take Ceclor for the full amount of time prescribed by your doctor, even if you feel better.

Shake your bottle well every time before taking Ceclor.

What is Ceclor?

Ceclor is used to treat infections caused by certain bacteria. It is an infections include middle ear, bladder, and skin infections, as well as strep throat, pneumonia and chronic bronchitis. Ceclor works by killing certain bacteria or preventing them from growing. It works only for certain bacteria and not for others. Your doctor may need to get results from laboratory tests or cultures to make sure you are taking the correct antibiotic. Ceclor will not work for colds, flu, or any viral infection. Ceclor is in a class of drugs known as cephalosporin antibiotics.

Who should not take Ceclor?

Do not take this drug if you are allergic to penicillin or any other cephalosporin-class antibiotic because it is likely that you may also be allergic to Ceclor.

Check with your doctor if you:

- have abdominal problems such as colitis
- are pregnant
- are breast-feeding
- are a diabetic and are checking your urine for sugar. (Ceclor can interfere with the urine test you may be using.)

How should I take Ceclor?

- Follow your doctor's advice about how to take Ceclor. Continue taking Ceclor even if you feel better. Be sure to take all of the medication for the length of time prescribed for you. If you stop taking your medication too soon, the bacteria can grow back and you may get sick again with the same infection.
- Shake your bottle well every time before taking this medicine.
- If you miss taking a dose of Ceclor, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and take your medicine as scheduled. Do not take double your prescribed dose.

What are the possible side effects of Ceclor?

The most common side effects are mild upset stomach, diarrhea, and rash. Call your doctor if these side effects persist or are bothersome.

Call your doctor immediately if the following side effects occur:

- Swelling of the throat or difficulty breathing
- Severe itching, and rash
- Severe or bloody diarrhea
- Abdominal pain
- Tiredness or faintness (that lasts after taking this medication for 24 hours)
- Fever (that lasts after taking this medication for 24 hours)
- Joint aches or stiffness (that lasts after taking this medication for 24 hours)

How should I store Ceclor?

- Keep Ceclor in the refrigerator.
- Throw away any unused portion after the expiration date.

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Ceclor. Medicines are sometimes prescribed for uses other than those listed in a Medication Guide. If you have any questions or concerns, or want more information about Ceclor, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Ceclor that is written for health professionals that you can ask to read.

[name of company]
[revision date]

This Medication Guide has been approved by the U.S. Food and Drug Administration.

PROTOTYPE

Medication Guide

Questions and Answers About

Cardizem

(generic name = diltiazem tablets)

What is the most important information that I should know about Cardizem?

Cardizem (pronounced KAR-de-zem) is used to treat angina pectoris (chest pain).

- Cardizem may lower your blood pressure. If you get dizzy while using Cardizem, call your doctor.
- Cardizem can interact with certain medications. Check with your doctor if you are taking a beta-blocker, cimetidine, or digitalis.
- You should not use Cardizem if you have certain heart conditions.
- If you notice very slow heart rate, palpitations, or feel very weak, call your doctor.

What is Cardizem?

Cardizem is used to treat angina pectoris (chest pain caused by narrowing of an artery in the heart). Cardizem relaxes or dilates blood vessels in the body. This increases blood flow to the heart and helps reduce chest pain. Cardizem is in a class of drugs known as calcium channel blockers.

Who should not take Cardizem?

- **If you have heart problems:** Your doctor needs to know if you have low blood pressure, heart block, a pacemaker, heart failure, or any other heart problem. Some patients with these conditions should not take Cardizem.
- **If you have liver or kidney problems:** Your doctor needs to know if you have any liver or kidney problems. Your doctor may need to monitor the effect of Cardizem on your liver or kidneys and may need to adjust the dose that you take.
- **If you are pregnant:** The use of Cardizem in pregnant women has not been studied. Studies with animals suggest, however, that Cardizem may cause miscarriages or stillbirths. Therefore, you should only use Cardizem during pregnancy if you and your doctor believe the benefits of using it outweigh the risks.
- **If you are nursing:** Cardizem is passed on to the child through breast milk. If you must take Cardizem, use some other form of infant feeding.

How should I take Cardizem?

You should take this medicine before meals if possible. If you miss taking a dose of Cardizem, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and take your medicine as scheduled. Do not take double your prescribed dose.

What should I avoid while taking Cardizem?

Cardizem can interact with several other medications. Your doctor may need to change the dosage of Cardizem or your other medicines. Check with your doctor before taking the following medicines:

- beta-blocker drugs (used for high blood pressure and other heart conditions);
- cimetidine (used for ulcers); and
- digitalis (used for heart failure or other heart problems).

What are the possible side effects of Cardizem?

The most common side effects of using Cardizem are edema (swelling of the legs), headache, dizziness, rash, and weakness.

A small number, (less than 1/2 percent), of patients taking Cardizem get heart palpitations, very slow heart rate or missed heart beats. If you notice a very slow heart beat, palpitations, or feel very weak, call your doctor.

Also, call your doctor if you have:

- Difficulty breathing (this may be a sign of heart failure)
- Dizziness (this may be a sign of low blood pressure).

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Cardizem. Medicines are sometimes prescribed for uses other than those listed in a Medication Guide. If you have any questions or concerns, or want more information about Cardizem, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Cardizem that is written for health professionals that you can ask to read.

[name of company]
[revision date]

This Medication Guide has been approved by the U.S. Food and Drug Administration.

PROTOTYPE

Medication Guide

C

Questions and Answers About

Halcion

(generic name = triazolam tablets)

What is the most important information I should know about Halcion?

Halcion (pronounced HAL-see-on) is used to help you sleep.

- **For many patients, Halcion should be used for a brief period (7 to 10 days). Halcion's effectiveness may decrease with longer use.**
- **Important risks of Halcion include: (1) memory problems, (2) withdrawal effects, (3) dependence, and (4) the possibility of serious mental and behavioral changes. The risk of these problems may increase with longer use.**
- **There are important cautions to consider while taking Halcion. Do not increase the dose or take other medicines without your doctor's advice. Avoid using alcohol. Avoid driving and other activities that require you to be alert until you know how this medication will affect you. Do not take Halcion if you are pregnant.**

What is Halcion?

Halcion treats insomnia (difficulty in falling asleep, frequent awakenings during the night, or early morning awakening). Halcion is in a class of drugs called benzodiazepines.

Who should not take Halcion?

Halcion should not be used during pregnancy. Some sleeping pills have been linked to birth defects when taken during the early months of pregnancy. Sedation and withdrawal effects have been seen in newborn infants of mothers who had taken sleeping pills late in pregnancy.

How should I take Halcion?

- **You should take Halcion only when 7 to 8 hours of sleep is possible.**
- **Take the dose your doctor prescribes. Do not increase the dose without consulting your doctor.**
- **Insomnia is often a short-term problem. It can be treated by a brief course of Halcion (7 to 10 days). When used for longer periods, Halcion's effectiveness may decrease and the risk of side effects may increase. You must discuss with your doctor the risks and benefits of continuing to use Halcion for more than a week.**

What should I avoid while taking Halcion?

- **Do not drink alcohol while taking Halcion.**
- **Halcion can make you sleepy, drowsy, dizzy, lightheaded, and less physically coordinated. Be careful doing anything hazardous that requires you to be mentally alert. Do not drive a car or operate any dangerous machinery until you know how the drug affects you.**
- **Check with your doctor before taking any other medicines. Be especially careful about any medicines that can make you drowsy.**

What are the possible side effects of Halcion?

Next-Day Drowsiness: All sleeping pills can make you drowsy the next day. Although Halcion may cause less next-day drowsiness than some other sleeping pills, you should take the lowest effective dose possible. Do not take Halcion when you need to be alert but cannot get 7 to 8 hours of sleep (for example, on a short airplane flight).

Memory Problems: All sleeping pills can cause memory loss (amnesia) for several hours after taking the drug. This is not generally a problem because people usually are asleep during this period. Halcion may be more likely than some other sleeping pills to cause memory loss. If you will need to be awakened within several hours after falling asleep, you should not take Halcion.

Withdrawal: All sleeping pills may have withdrawal effects when they are stopped. Halcion may be more likely than some other sleeping pills to have such problems. When Halcion is stopped, you may temporarily have worse insomnia than when you started. Another withdrawal effect includes unpleasant feelings. Less common withdrawal effects include abdominal and muscle cramps, vomiting, sweating, tremors (shakes), and rarely, convulsions. Withdrawal effects are more common and more severe after longer use.

Withdrawal effects between doses. You may have more problems [illegible] third of the night or you may be nervous during the day.

Dependence: Halcion is used for more than a few weeks, you may become "dependent" upon the drug. You may feel increased urgency to continue to take it or to increase the dose.

Mental and Behavior Changes: Changes in thinking and behavior have been reported by people taking Halcion and other sleeping pills. As with alcohol intoxication, sometimes people taking Halcion become more uninhibited, outgoing, or aggressive. More unusual changes include confusion, strange behavior, agitation, hallucinations, worsening of depression, and suicidal thinking. It is not known if these more unusual changes are caused by the drug, by some underlying illness, or have another cause. It is important to discuss any such changes in thinking or behavior with your doctor.

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Halcion. Medicines are sometimes prescribed for uses that are not listed in a Medication Guide. If you have any questions or concerns, or want more information about Halcion, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Halcion that is written for health professionals that you can ask to read.

[name of company]
[revision date]

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Medication Guide

Questions and Answers About

Diltiazem tablets

What is the most important information that I should know about Diltiazem?

Diltiazem (pronounced DIL-tie-a-zehm) is used to treat angina pectoris (chest pain).

- Diltiazem may lower your blood pressure. If you get dizzy while using Diltiazem, call your doctor.
- Diltiazem can interact with certain medications. Check with your doctor if you are taking a beta-blocker, cimetidine, or digitalis.
- You should not use Diltiazem if you have certain heart conditions.
- If you notice very slow heart rate, palpitations, or feel very weak, call your doctor.

What is Diltiazem?

Diltiazem is used to treat angina pectoris (chest pain caused by narrowing of an artery in the heart). Diltiazem relaxes or dilates blood vessels in the body. This increases blood flow to the heart and helps relieve pain. Diltiazem is in a class of drugs known as calcium channel blockers.

Who should not take Diltiazem?

- If you have heart problems: Your doctor needs to know if you have low blood pressure, heart block, a pacemaker, heart failure, or any other heart problem. Some patients with these conditions should not take Diltiazem.
- If you have liver or kidney problems: Your doctor needs to know if you have any liver or kidney problems. Your doctor may need to monitor the effect of Diltiazem on your liver or kidneys and may need to adjust the dose that you take.
- If you are pregnant: The use of Diltiazem in pregnant women has not been studied. Studies with animals suggest, however, that Diltiazem may cause miscarriages or stillbirths. Therefore, you should only use Diltiazem during pregnancy if you and your doctor believe the benefits of using it outweigh the risks.
- If you are nursing: Diltiazem is passed on to the child through breast milk. If you must take Diltiazem, use some other form of infant feeding.

How should I take Diltiazem?

You should take this medicine before meals if possible. If you miss taking a dose of Diltiazem, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and take your medicine as scheduled. Do not take double your prescribed dose.

What should I avoid while taking Diltiazem?

Diltiazem can interact with several other medications. Your doctor may need to change the dosage of Diltiazem or your other medicines. Check with your doctor before taking the following medicines:

- beta-blocker drugs (used for high blood pressure and other heart conditions);
- cimetidine (used for ulcers); and
- digitalis (used for heart failure or other heart problems).

What are the possible side effects of Diltiazem?

The most common side effects of using Diltiazem are edema (swelling of the [illegible]), headache, dizziness, rash, and weakness.

Rarely (less than 1/2 percent), patients taking Diltiazem get chest palpitations, very slow heart rate or missed heart beats. If you notice a very slow heart beat, palpitations, or feel very weak, call your doctor.

Also, call your doctor if you have:

- Difficulty breathing (this may be a sign of heart failure)
- Dizziness (this may be a sign of low blood pressure).

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Diltiazem. Medicines are sometimes prescribed for uses other than those listed in a Medication Guide. If you have any questions or concerns, or want more information about Diltiazem, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Diltiazem that is written for health professionals that you can ask to read.

[name of company]
[address]

This Medication Guide has been approved by the U.S. Food and Drug Administration.

BILLING CODE 4160–01–C

Appendix C—Several Sample Medication Guides Using Alternative Formats

Medication Guide

Ceclor

(generic name = cefaclor for oral suspension)

Summary

Ceclor (pronounced SEE-Klor) is used to treat infections caused by certain bacteria. You should not take Ceclor if you are allergic to penicillin or other similar antibiotics. Allergic reactions to Ceclor, as with other drugs, can be fatal. If you experience difficulty breathing, swelling of the throat, rash, or severe diarrhea or abdominal pain, call your doctor immediately or seek medical help.

Take Ceclor for the full amount of time prescribed by your doctor, even if you feel better.

Shake your bottle well every time before taking Ceclor.

Uses

Ceclor is used to treat infections caused by certain bacteria. These infections include middle ear, bladder, and skin infections, as well as strep throat, pneumonia and chronic bronchitis. Ceclor works by killing certain bacteria or preventing them from growing. It works only for certain bacteria and not for others. Your doctor may need to get results from laboratory tests or cultures to make sure you are taking the correct antibiotic. Ceclor will not work for colds, flu, or any viral infection. Ceclor is in a class of drugs known as cephalosporin antibiotics.

General Cautions

- Do not take this drug if you are allergic to penicillin or any other cephalosporin-class antibiotic because it is likely that you may also be allergic to Ceclor.

Check with your doctor if you

- have abdominal [illegible] as colitis
- are pregnant
- are breast-feeding
- are a diabetic and are checking your urine for sugar. (Ceclor can interfere with the urine test you may be using.)

Proper Use

- Follow your doctor's advice about how to take Ceclor. Continue taking Ceclor even if you feel better. Be sure to take all of the medication for the length of time prescribed for you. If you stop taking your medication too soon, the bacteria can grow back and you may get sick again with the same infection.
- Shake your bottle well every time before taking this medicine.
- If you miss taking a dose of Ceclor, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and take your medicine as scheduled. Do not take double your prescribed dose.

Possible Side Effects

The most common side effects are mild upset stomach, diarrhea, and rash. Call your doctor if these side effects persist or are bothersome.

Call your doctor immediately if [illegible] side effects occur:

- [illegible] the throat or difficulty breathing
- Hives, itching, and rash
- Severe or bloody diarrhea
- Abdominal pain
- Tiredness or faintness (that lasts after taking this medication for 24 hours)
- Fever (that lasts after taking this medication for 24 hours)
- Joint aches or stiffness (that lasts after taking this medication for 24 hours)

Storage

- Keep Ceclor in the refrigerator.
- Throw away any unused portion after the expiration date.

Each teaspoon (5ml) of Ceclor for Oral Suspension contains either 125, 250, or 375 mg of cefaclor monohydrate and is pink in color.

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Ceclor. Medicines are sometimes prescribed for uses other than those listed in a Medication Guide. If you have any questions or concerns, or want more information about Ceclor, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Ceclor that is written for health professionals that you can ask to read.

[name of company]
[revision date]

This Medication Guide has been approved by the U.S. Food and Drug Administration.

PROTOTYPE

Medication Guide

Cardizem

(generic name = diltiazem tablets)

Summary

Cardizem (pronounced KAR-de-zem) is used to treat angina pectoris (chest pain).

- **Cardizem may lower your blood pressure. If you get dizzy while using Cardizem, call your doctor.**
- **Cardizem can interact with certain medications. Check with your doctor if you are taking a beta-blocker, cimetidine, or digitalis.**
- **You should not use Cardizem if you have certain heart conditions.**
- **If you notice very slow heart rate, palpitations, or feel very weak, call your doctor.**

Uses

Cardizem is used to treat angina pectoris (chest pain caused by narrowing of an artery in the heart). Cardizem relaxes or dilates blood vessels in the body. This increases blood flow to the heart and helps reduce chest pain. Cardizem is in a class of drugs known as calcium channel blockers.

Cautions

- **Heart Problems:** Your doctor needs to know if you have low blood pressure, heart block, a pacemaker, heart failure, or any other heart problem. Some patients with these conditions should not take Cardizem.
- **Liver or Kidney Problems:** Your doctor needs to know if you have any liver or kidney problems. Your doctor may need to monitor the effect of Cardizem on your liver or kidneys and may need to adjust the dose that you take.
- **Pregnancy:** The use of Cardizem in pregnant women has not been studied. Studies in animals suggest, however, that Cardizem may cause miscarriages or stillbirths. Therefore, you should only use Cardizem during pregnancy if you and your doctor believe the benefits of using it outweigh the risks.
- **Nursing Mothers:** Cardizem is passed on to the child through breast milk. If you must take Cardizem, use some other form of infant feeding.

Cardizem can interact with several other medications. Your doctor may need to change the dosage of Cardizem or your other medicines. **Check with your doctor before taking the following medicines:**

- beta-blocker drugs (used for high blood pressure and other heart conditions);
- cimetidine (used for ulcers); and
- digitalis (used for heart failure or other heart problems).

Proper Use

You should take this medicine before meals if possible. If you miss taking a dose of Cardizem, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and take your medicine as scheduled. Do not double your prescribed dose.

Possible Side Effects

The most common side effects of [illegible] are edema (swelling of the legs), headache, dizziness, rash, and weakness.

A small number, (less than 1/2 percent), of patients taking Cardizem get heart palpitations, very slow heart rate or missed heart beats. **If you notice a very slow heart beat, palpitations, or feel very weak, call your doctor.**

Also, call your doctor if you have:

- **Difficulty breathing (this may be a sign of heart failure)**
- **Dizziness (this may be a sign of low blood pressure).**

Each 30mg tablet is green and round, engraved with MARION on one side an 1771 on the other. Each 60mg tablet is yellow and round, engraved with MARION on one side and 1772 on the other. Each 90mg tablet is green and oblong, engraved with CARDIZEM on one side and 90mg on the other. Each 120mg tablet is yellow and oblong, engraved with CARDIZEM on one side and 120mg on the other.

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Cardizem. Medicines are sometimes prescribed for uses other than those listed in a Medication Guide. If you have any questions or concerns, or want more information about Cardizem, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Cardizem that is written for health professionals that you can ask to read.

[name of company]
[revision date]

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Medication Guide

Halcion

(generic name = triazolam tablets)

Summary

Halcion (pronounced HAL-see-on) is used to help you sleep.

- For many patients, Halcion should be used for a brief period (7 to 10 days). Halcion's effectiveness may decrease with longer use.
- Important risks of Halcion include: (1) memory problems, (2) withdrawal effects, (3) dependence, and (4) the possibility of serious mental and behavioral changes. The risk of these problems may increase with longer use.
- There are important cautions to consider while taking Halcion. Do not increase the dose or take other medicines without your doctor's advice. Avoid using alcohol. Avoid driving and other activities that require you to be alert until you know how this medication will affect you. Do not take Halcion if you are pregnant.

Uses

Halcion treats insomnia (difficulty in falling asleep, frequent awakening during the night, or early morning awakening). Halcion is in a class of drugs called benzodiazepines.

General Cautions

- Halcion should not be used during pregnancy. Some sleeping pills have been linked to birth defects when taken during the early months of pregnancy. Sedation and withdrawal effects have been seen in newborn infants of mothers who had taken sleeping pills late in pregnancy.
- Do not drink alcohol while taking Halcion.
- Halcion can make you sleepy, drowsy, dizzy, lightheaded, and less physically coordinated. Be careful doing anything hazardous that requires you to be mentally alert. Do not drive a car or operate any dangerous machinery until you know how the drug affects you.
- Check with your doctor before taking any other medicines. Be especially careful about any medicines that can make you drowsy.

Proper Use

You should take Halcion only when 7 to 8 hours of sleep is possible. Take the dose your doctor prescribes. Do not increase the dose without consulting your doctor. Insomnia is often a short-term problem. It can be treated by a brief course of Halcion (7 to 10 days). When used for longer periods, Halcion's effectiveness may decrease and the risk of side effects may increase. You must discuss with your doctor the risks and benefits of continuing to use Halcion for more than a week.

Possible Side Effects

Next-Day Drowsiness: All sleeping pills can make you drowsy the next day. Although Halcion may cause less next-day drowsiness than some other sleeping pills, you should take the lowest effective dose possible. Do not take Halcion when you need to be alert but cannot get 7 to 8 hours of sleep (for example, on a short airplane flight).

Memory Problems: All sleeping pills can cause memory loss (amnesia) for several hours after taking the drug. This is not generally a problem because people are usually asleep during this period. Halcion may be more likely than some other sleeping pills to cause memory loss. If you will need to be awakened within several hours after falling asleep, you should not take Halcion.

Withdrawal: All sleeping pills may have withdrawal effects when they are stopped. Halcion may be more likely than some other sleeping pills to have such problems. When Halcion is stopped, you may temporarily have worse insomnia than when you started [illegible] withdrawal effect [illegible] unpleasant feelings. Less common withdrawal effects include abdominal and muscle cramps, vomiting, sweating, tremors (shakes), and rarely, convulsions. Withdrawal effects are more common and more severe after longer use.

Halcion may cause withdrawal effects between doses. You may have more problems sleeping during the last third of the night or you may be nervous during the day.

Dependence: If Halcion is used for more than a few weeks, you may become "dependent" upon the drug. You may feel increased urgency to continue to take it or to increase the dose.

Mental and Behavior Changes: Changes in thinking and behavior have been reported by people taking Halcion and other sleeping pills. As with alcohol intoxication, sometimes people become more uninhibited, outgoing, or aggressive. More unusual changes include confusion, strange behavior, agitation, hallucinations, worsening of depression, and suicidal thinking. It is not known if these more unusual changes are caused by the drug, by some underlying illness, or have another cause. It is important to discuss any such changes in thinking or behavior with your doctor.

Each 0.125 mg tablet is white and round, engraved with HALCION .125 on one side and 10 on the other. Each 0.25 mg tablet is green and round, with HALCION .25 on one side and 17 on the other.

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Halcion. Medicines are sometimes prescribed for uses other than those listed in a Medication Guide. If you have any questions or concerns, or want more information about Halcion, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Halcion that is written for health professionals that you can ask to read.

[name of company]
[revision date]

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Medication Guide

Diltiazem tablets

Summary

Diltiazem (pronounced Dill-tie-a-zehm) is used to treat angina pectoris (chest pain).

- Diltiazem may lower your blood pressure. If you get dizzy while using Diltiazem, call your doctor.
- Diltiazem can interact with certain medications. Check with your doctor if you are taking a beta-blocker, cimetidine, or digitalis.
- You should not use Diltiazem if you have certain heart conditions.
- If you notice very slow heart rate, palpitations, or feel very weak, call your doctor.

Uses

Diltiazem is used to treat angina pectoris (chest pain caused by narrowing of an artery in the heart). Diltiazem relaxes or dilates blood vessels in the body. This increases blood flow to the heart and helps reduce chest pain. Diltiazem is in a class of drugs known as calcium channel blockers.

Cautions

- **Heart Problems:** Your doctor needs to know if you have low blood pressure, heart block, a pacemaker, heart failure, or any other heart problem. Some patients with these conditions should not take Diltiazem.
- **Liver or Kidney Problems:** Your doctor needs to know if you have any liver or kidney problems. Your doctor may need to monitor the effect of Diltiazem on your liver or kidneys and may need to adjust the dose that you take.
- **Pregnancy:** The use of Diltiazem in pregnant women has not been studied. Studies with animals suggest, however, that Diltiazem may cause birth defects or stillbirths. Therefore, you should only use Diltiazem during pregnancy if you and your doctor believe the benefits of using it outweigh the risks.
- **Nursing Mothers:** Diltiazem is passed on to the child through breast milk. If you must take Diltiazem, use some other form of infant feeding.

Diltiazem can interact with several other medications. Your doctor may need to change the dosage of Diltiazem or your other medicines. Check with your doctor before taking the following medicines:

- beta-blocker drugs (used for high blood pressure and other heart conditions);
- cimetidine (used for ulcers); and
- digitalis (used for heart failure or other heart problems).

Proper Use

You should take this medicine before meals if possible. If you miss taking a dose of Diltiazem, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and take your medicine as scheduled. Do not double your prescribed dose.

Possible Side Effects

The most common side effects of using Diltiazem are edema (swelling of the legs), headache, dizziness, rash, and weakness.

A small number, (less than 1/2 [illegible] patients taking Diltiazem may [illegible] heart palpitations, very [illegible] heart rate or missed heart beats. If you notice a very slow heart beat, palpitations, or feel very weak, call your doctor.

Also, call your doctor if you have:

- Difficulty breathing (this may be a sign of heart failure)
- Dizziness (this may be a sign of low blood pressure).

Each 30mg tablet is green and round, engraved with COPLEY 631. Each 60mg tablet is yellow and round, engraved with COPLEY 662. Each 90mg tablet is green and oblong, engraved with COPLEY 691. Each 120mg tablet is yellow and oblong, engraved with COPLEY 720.

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Diltiazem. Medicines are sometimes prescribed for uses other than those listed in a Medication Guide. If you have any questions or concerns, or want more information about Diltiazem, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Diltiazem that is written for health professionals that you can ask to read.

[illegible]

This Medication Guide has been approved by the U.S. Food and Drug Administration.

PROTOTYPE

Medication Guide

Ceclor

(generic name = cefaclor for oral suspension)

What is the most important information I should know about Ceclor?

Ceclor (pronounced SEE-klor) is used to treat infections caused by certain bacteria. You should not take Ceclor if you are allergic to penicillin or other similar antibiotics. Allergic reactions to Ceclor, as with other drugs, can be fatal. If you experience difficulty breathing, swelling of the throat, rash, or severe diarrhea or abdominal pain, call your doctor immediately or seek medical help.

Take Ceclor for the full amount of time prescribed by your doctor, even if you feel better.

Shake your bottle well every time before taking Ceclor.

Ceclor is used to treat infections caused by certain bacteria. These infections include middle ear, bladder, and skin infections, as well as strep throat, pneumonia and chronic bronchitis. Ceclor works by killing certain bacteria or preventing them from growing. It works only for certain bacteria and not for others. Your doctor may need to get results from laboratory tests or cultures to make sure you are taking the correct antibiotic. Ceclor will not work for colds, flu, or any viral infection. Ceclor is in a class of drugs known as cephalosporin antibiotics.

Before Taking Your Medicine

Check with your doctor if you:

have abdominal problems such as colitis

are pregnant

are nursing

are a diabetic and checking your urine for sugar: Ceclor can interfere with the urine test you may be using to test for sugar.

are taking other medications: Do not take this drug if you are allergic to penicillin or any other cephalosporin-class antibiotic because it is likely that you may also be allergic to Ceclor.

While You Are Taking Your Medicine

Continue taking Ceclor even if you feel better. Be sure to take all of the medication for the length of time prescribed for you. If you stop taking your medication too soon, the bacteria can grow back and you may get sick again with the same infection. If you miss taking a dose of Ceclor, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and take your medicine as scheduled. Do not take double your prescribed dose.

The most common side effects are mild upset stomach, diarrhea, and rash. Call your doctor if these side effects persist or are bothersome.

Call your doctor if the following side effects occur:

- Swelling of the throat or difficulty breathing
- Hives, itching, and rash
- Severe or bloody diarrhea
- Abdominal pain
- Tiredness or faintness (that lasts after taking this medication)
- Fever (that lasts after taking this medication for 24 hours)
- Joint aches or stiffness (that lasts after taking this medication for 24 hours)

Shake your bottle well every time before taking this medicine.

Keep Ceclor in the refrigerator. Throw away any unused portion after the expiration date.

Each teaspoon (5ml) of Ceclor for Oral Suspension contains either 125, 250, or 375 mg of cefaclor monohydrate and is pink in color.

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Ceclor. Medicines are sometimes prescribed for uses other than those listed in a Medication Guide. If you have any questions or concerns, or want more information about Ceclor, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Ceclor that is written for health professionals that you can ask to read.

[name of company]
[revision date]

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Medication Guide

Cardizem

(generic name = diltiazem tablets)

What is the most important information that I should know about Cardizem?

Cardizem (pronounced KAR-de-zem) is used to treat angina pectoris (chest pain).

- Cardizem may lower your blood pressure. If you get dizzy while using Cardizem, call your doctor.
- Cardizem can interact with certain medications. Check with your doctor if you are taking a beta-blocker, cimetidine, or digitalis.
- You should not use Cardizem if you have certain heart conditions.
- If you notice very slow heart rate, palpitations, or feel very weak, call your doctor.

Cardizem is used to treat angina pectoris (chest pain caused by narrowing of an artery in the heart). Cardizem relaxes or dilates blood vessels in the body. This increases blood flow to the heart and helps reduce chest pain. Cardizem is in a class of drugs known as calcium channel blockers.

Before Taking Your Medicine

If you have heart problems: Your doctor needs to know if you have low blood pressure, heart block, a pacemaker, heart failure, or any other heart problem. Some patients with these conditions should not take Cardizem.

If you have liver or kidney problems: Your doctor needs to know if you have any liver or kidney problems. Your doctor may need to monitor the effect of Cardizem on your liver or kidneys and may need to adjust the dose that you take.

If you are pregnant: The use of Cardizem in pregnant women has not been studied. Studies with animals suggest, however, that Cardizem may cause miscarriages or stillbirths. Therefore, you should only use Cardizem during pregnancy if you and your doctor believe the benefits of using it outweigh the risks.

If you are nursing: Cardizem is passed on to the child through breast milk. If you must take Cardizem, use some other form of infant feeding.

If you are taking other medications: Cardizem can interact with other medications. Your doctor may need to change the dosage of Cardizem or your other medicines. Check with your doctor before taking the following medicines:

- beta-blocker drugs (used for high blood pressure and other heart conditions);
- cimetidine (used for ulcers); and
- digitalis (used for heart failure or other heart problems)

While You Are Taking Your Medicine

You should take this medicine before meals if possible. If you miss taking a dose of Cardizem, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and take your medicine as scheduled. Do not take double your prescribed dose.

Call your doctor if the following side effects occur:

The most common side effects of using Cardizem are edema (swelling of the legs), headache, dizziness, rash, and weakness.

A small number, (less than 1/2 percent), of patients taking Cardizem get heart palpitations, very slow heart rate or missed heart beats. If you notice a very slow heart beat, palpitations, or feel very weak, call your doctor.

Also call your doctor if you have:

- Difficulty breathing (this may be a sign of heart failure)
- Dizziness (this may be a sign of low blood pressure).

Each 30mg tablet is green and round, engraved with MARION on one side and 1771 on the other. Each 60mg tablet is yellow and round, engraved with MARION on one side and 1772 on the other. Each 90mg tablet is green and oblong, engraved with CARDIZEM on one side and 90mg on the other. Each 120mg tablet is yellow and oblong, engraved with CARDIZEM on one side and 120mg on the other.

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Cardizem. Medicines are sometimes prescribed for uses other than those listed in a Medication Guide. If you have any questions or concerns, or want more information about Cardizem, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Cardizem that is written for health professionals that you can ask to read.

[name of company]
[revision date]

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Medication Guide

Halcion

(generic name = triazolam tablets)

What is the most important information I should know about Halcion?

Halcion (pronounced HAL-see-on) is used to help you sleep.

- For many patients, Halcion should be used for a brief period (7 to 10 days). Halcion's effectiveness may decrease with longer use.
- Important risks of Halcion include: (1) memory problems, (2) withdrawal effects, (3) dependence, and (4) the possibility of serious mental and behavioral changes. The risk of these problems may increase with longer use.
- There are important cautions to consider while taking Halcion. Do not increase the dose or take other medicines without your doctor's advice. Avoid using alcohol. Avoid driving or other activities that require you to be alert until you know how this medication will affect you. Do not take Halcion if you are pregnant.

Halcion treats insomnia (difficulty in falling asleep, frequent awakening during the night, or early morning awakening). Halcion is in a class of drug called benzodiazepines.

Before Taking Your Medicine

If you are pregnant: Halcion should not be used during pregnancy. Some sleeping pills have been linked to birth defects when taken during the early months of pregnancy. Sedation and withdrawal effects have been seen in newborn infants of mothers who had taken sleeping pills late in pregnancy.

While You Are Taking Your Medicine

- You should take Halcion only when 7 to 8 hours of sleep is possible.
- Take the dose your doctor prescribes. Do not increase the dose without consulting your doctor.
- Insomnia is often a short-term problem. It can be treated by a brief course of Halcion (7 to 10 days). When used for longer periods, Halcion's effectiveness may decrease and the risk of side effects may increase. You must discuss with your doctor the risks and benefits of continuing to use Halcion for more than a week.
- Do not drink alcohol while taking Halcion.
- Halcion can make you sleepy, drowsy, dizzy, lightheaded, and less physically coordinated. Be careful doing anything hazardous that requires you to be mentally alert. Do not drive a car or operate any dangerous machinery until you know how the drug affects you.
- Check with your doctor before taking any other medicines. Be especially careful about any medicines that can make you drowsy.

Call your doctor if the following side effects occur:

Next-Day Drowsiness: All sleeping pills can make you drowsy the next day. Although Halcion may cause less next-day drowsiness than some other sleeping pills, you should take the lowest effective dose possible. Do not take Halcion when you need to be alert but cannot get 7 to 8 hours of sleep (for example, on a short airplane flight).

Memory Problems: All sleeping pills can cause memory loss (amnesia) for several hours after taking the drug. This is not generally a problem because people usually are asleep during this period. Halcion may be more likely than some other sleeping pills to cause memory loss. If you will need to be awakened within several hours after falling asleep, you should not take Halcion.

Withdrawal: All sleeping pills may have withdrawal effects when they are stopped. Halcion may be more likely than some other sleeping pills to have such problems. When Halcion is stopped, you may temporarily have worse insomnia than when you started. Another withdrawal effect includes unpleasant feelings. Less common withdrawal effects include abdominal and muscle cramps, vomiting, sweating, tremors (shakes), and rarely, convulsions. Withdrawal effects are more common and more severe after longer use.

Halcion may cause withdrawal effects between doses. You may have more problems sleeping during the last third of the night or you may be nervous during the day.

Dependence: If Halcion is used for more than a few weeks, you may become [illegible] upon the drug. You may feel increased urgency to continue to take it [illegible] the dose.

[illegible] Behavior Changes: Changes in thinking and behavior have been reported by people taking Halcion and other sleeping pills. As with alcohol intoxication, sometimes people taking Halcion become more uninhibited, outgoing, or aggressive. More unusual changes include confusion, strange behavior, agitation, hallucinations, worsening of depression, and suicidal thinking. It is not known if these more unusual changes are caused by the drug, by some underlying illness, or have another cause. It is important to discuss any such changes in thinking or behavior with your doctor.

Each 0.125 mg tablet is white and round engraved with HALCION .125 on one side and 10 on the other. Each 0.25 mg tablet is green and round with HALCION .25 on one side and 17 on the other.

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Halcion. Medicines are sometimes prescribed for uses not listed in a Medication Guide. If you have any questions or concerns, or want more information about Halcion, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Halcion that is written for health professionals that you can read.

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Medication Guide

Diltiazem tablets

What is the most important information that I should know about Diltiazem?

Diltiazem (pronounced DIL-ite-a-zehm) is used to treat angina pectoris (chest pain).

- Diltiazem may lower your blood pressure. If you get dizzy while using Diltiazem, call your doctor.
- Diltiazem can interact with certain medications. Check with your doctor if you are taking a beta-blocker, cimetidine, or digitalis.
- You should not use Diltiazem if you have certain heart conditions.
- If you notice very slow heart rate, palpitations, or feel very weak, call your doctor.

Diltiazem is used to treat angina pectoris (chest pain caused by narrowing of an artery in the heart). Diltiazem relaxes or dilates blood vessels in the body. This increases blood flow to the heart and helps relieve chest pain. Diltiazem is in a class of drugs known as calcium channel blockers.

Before Taking Your Medicine

If you have heart problems: Your doctor needs to know if you have low blood pressure, heart block, a pacemaker, heart failure, or any other heart problem. Some patients with these conditions should not take Diltiazem.

If you have liver or kidney problems: Your doctor needs to know if you have any liver or kidney problems. Your doctor may need to monitor the effect of Diltiazem on your liver or kidneys and may need to adjust the dose that you take.

If you are pregnant: The use of Diltiazem in pregnant women has not been studied. Studies with animals suggest, however, that Diltiazem may cause miscarriages or stillbirths. Therefore, you should only use Diltiazem during pregnancy if you and your doctor believe the benefits of using it outweigh the risks.

If you are nursing: Diltiazem is passed on to the child through breast milk. If you must take Diltiazem, use some other form of infant feeding.

If you are taking other medications: Diltiazem can interact with other medications. Your doctor may need to change the dosage of Diltiazem or your other medicines. Check with your doctor before taking the following medicines:

- beta-blocker drugs (used for high blood pressure and other heart conditions);
- cimetidine (used for ulcers); and
- digitalis (used for heart failure or other heart problems)

While You Are Taking Your Medicine

You should take this medicine before meals if possible. If you miss taking a dose of Diltiazem, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and take your medicine as scheduled. Do not take double your prescribed dose.

Call your doctor if the following side effects occur:

The most common side effects of using Diltiazem are edema (swelling of the legs), headache, dizziness, rash, and weakness.

A small number, (less than 1/2 percent), of patients taking Diltiazem get heart palpitations, very slow heart rate or missed heart beats. If you notice heart palpitations, very slow heart beat, palpitations, or feel very weak, call your doctor.

Call your doctor if you have:

- Difficulty breathing (this may be a sign of heart failure)
- Dizziness (this may be a sign of low blood pressure).

Each 30mg tablet is green and round, engraved with COPLEY 631. Each 60mg tablet is yellow and round, engraved with COPLEY 662. Each 90mg tablet is green and oblong, engraved with COPLEY 691. Each 120mg tablet is yellow and oblong, engraved with COPLEY 720.

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Diltiazem. Medicines are sometimes prescribed for uses other than those listed in a Medication Guide. If you have any questions or concerns, or want more information about Diltiazem, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Diltiazem that is written for health professionals that you can ask to read.

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